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PETECHIAL HEMORRHAGES OF THE BRAIN

EXPERIMENTALLY PRODUCED IN RATS BY CONCUSSION

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In a previous study [1] we investigated the nature of traumatic petechial hemorrhages in 11 human brains, the interval of survival after trauma varying from an unmeasurable period, designated for lack of a better term, perhaps improperly, as "immediate death," to eight days. All brains, studied by careful histologic methods, showed perivascular petechiae. They were frequent about the arterioles. The different forms and states of petechiae, as well as their location in the brain substance, were described. A theory was advanced as to the formation of ring and ball hemorrhages from fresh petechiae. The data obtained led to the conclusion that multiple petechial hemorrhages are a characteristic finding in cases of severe concussion of the brain and are dependent on vasodilatation, vascular stasis (prestasis) and anoxemia, and that mild, reversible concussion effects on the parenchyma of the brain should be distinguished from severe, irreversible concussion effects. The possible relationship of severe concussion effects to traumatic encephalopathy, late (traumatic) apoplexy and softening was discussed.

A further study of the nature and significance of multiple petechial hemorrhages in brains of traumatized animals is here reported.

MATERIAL AND METHODS

Albino rats, aged 100 days or over, were selected as desirable experimental animals. These were healthy animals, such as are used in routine experiments

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1. Schaller, W. F.; Tamaki, K., and Newman, H. W.: Nature and Significance of Multiple Petechial Hemorrhages Associated with Trauma of the Brain, Arch. Neurol. & Psychiat. **37**:1048-1076 (May) 1937.

in the Stanford laboratories. Twenty-seven rats were used in the experiments, 7 of which served as normal controls. The apparatus for producing trauma has been described in a previous article (fig. 1). The body of the animal was suspended in a zipper pocket at the end of a lever, which fell of its own weight. The exposed head of the animal (vertex) could thus be subjected to different degrees of trauma by varying the fall of the lever. It was found that when the lever was dropped from a designated point on the stanchion, representing a fall of 67 cm., the blow was fatal. A fall of from 50 to 60 cm. usually caused a severe but not fatal concussion, and a fall of 27 cm. a slight concussion effect. The traumas to which these animals were subjected also varied from single or repeated falls in the initial experiment to repeated falls at subsequent intervals. A number of animals were killed by means of ether immediately after trauma,

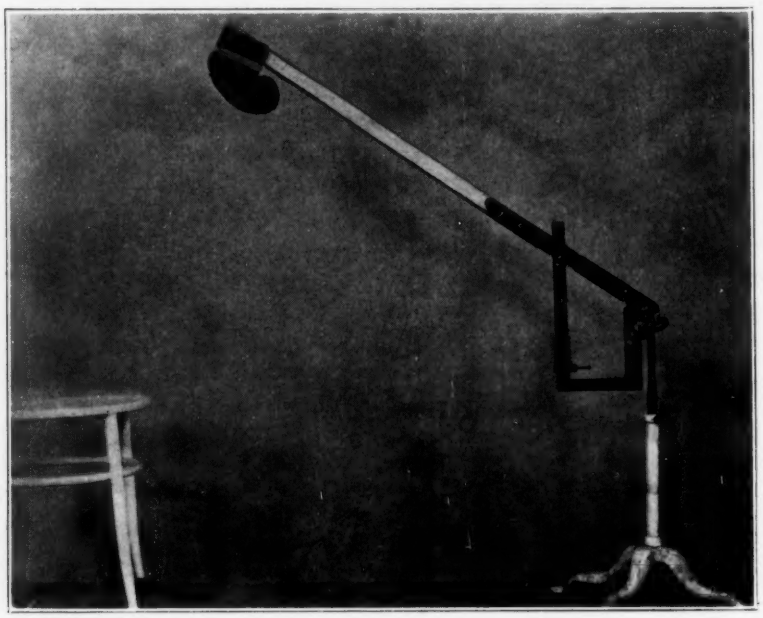

Fig. 1.—Apparatus for producing trauma to the head in the white rat.

and others at varying intervals after the last trauma. The longest interval between the initial trauma and death was two hundred and eighty-two days.

Our experiments may be divided into two series of essentially similar nature; the first is incomplete, owing to a laboratory mishap. The second consisted of a series of 5 normal controls and of 5 animals which were killed, on an average, two months after trauma. In all the control studies and in the first series, except when specially noted, the brains were exposed after death by removal of the skull cap and fixed in situ either in a 10 per cent solution of formaldehyde or in a solution of formobromide, and later prepared for embedding in pyroxylin. In the second series the traumatized brains were removed from the skull before fixation. Hematoxylin and eosin and the hematoxylin-Van Gieson method were used as routine stains of serial longitudinal microscopic sections, which averaged from 12 to 20 microns in thickness; in the first series the sections were numbered

from the vertex to the base. Special stains, including the gold and silver impregnation methods for studies of the glia in relation to petechiae, were employed as indicated. Every fifth section was stained, and in exceptional cases every tenth section. In some cases the whole brain was sectioned in a block; in others the hemispheres were divided and only one hemisphere was sectioned serially, the remaining hemisphere being preserved for further studies of the brain parenchyma. An attempt to estimate changes in the size of vessels following trauma by means of micrometry through comparison with the controls was abandoned as impracticable.

RESULTS

Petechial hemorrhages were produced in these traumatized animals which in all respects were similar to those observed in traumatized human brains. Their relative size and frequency in veins, arterioles and capillaries were noted, as well as the part of the brain chiefly involved. As the rate of growth and tissue repair in the albino rat is thirty times that in man (Donnelson), the histologic changes in our experimental animals may be regarded as an intensified picture of the human process.

SERIES ONE

Group 1.—Normal controls: 7 animals (5 in first series; 2 in second series).

Group 2.—Death directly following and resulting from trauma: 5 animals.

Group 3.—Death at a definite interval after trauma. (*a*) Induced after single or repeated traumas in initial experiment: 8 animals. (*b*) Induced after repeated traumas on successive days: 2 animals.

Group 1. Normal Controls (animals B 18, B 19, C 1, C 2, C 3, C 4 and C 5).—In this study, controls for series 1 and 2 are reported together. Healthy, untraumatized white rats, 100 days old, served as controls for the experiments. Death occurred from four to seven minutes after commencement of etherization. The skull was opened and the intact brain exposed; the head and the brain in situ were placed in 10 per cent solution of formaldehyde. The time between death and introduction into the solution averaged from four to five minutes. In the case of animals B 18 and B 19 the whole brain was sectioned; the brains of the other controls were divided into halves, a sagittal cut dividing the hemispheres and the cerebellum. One half of the brain was then embedded in pyroxylin and cut in serial longitudinal sections. Of every five sections, the first was stained with hematoxylin and eosin and the second by the hematoxylin-Van Gieson technic. The other half of the brain was preserved for future control studies.

Moderate extravascular meningeal and ventricular accumulation of red cells was of practically constant occurrence; dilatation of vessels and shredding and vacuolation in the white matter were frequently observed. Staining the vacuolated areas for oligodendroglia by the combined method of Penfield revealed that these spaces were empty, thus eliminating the possibility that swollen oligodendroglia cells occupied these spaces in sections not selectively stained. In animal C 1 a vessel in the neighborhood of the right internal capsule showed a few red cells outside the wall, as traced through twenty sections. This vessel approached the ventricular wall, in which a hemorrhage was noted. The red cells were limited to a particular section of the circumference of the vessel and rapidly diminished in number as the distance from the ventricle increased.

Some perivascular accumulation of red cells was occasionally observed in relation to the cut brain surfaces, as in animals C 2 and C 3. In animal C 4 a small perivascular hemorrhage was noted in the tegmentum and also in the subcortical white matter of the frontal lobe. In animal C 5 a small perivascular hemorrhage was traced serially to the meninges. The brain of this control animal showed many dilated veins, which in pathologic material might have been considered abnormal. In animal C 3 definitely thickened arterial walls were seen.

The foregoing control studies, therefore, did not present a picture of traumatic perivascular diapedesis hemorrhage, in character, location or extent. The meningeal and ventricular hemorrhages could be explained as artificially produced by removal and cutting of the formaldehyde-fixed brain, and the small associated diapedesis hemorrhages as due to squeezing or bruising and consequent direct extension into the vessel sheath. In only 1 control were two deeper perivascular diapedesis hemorrhages seen; these were small and limited strictly to the perivascular space.

Nowhere were there found extensive accumulations resulting from diapedesis, such as are seen in pathologic material. Ball and ring hemorrhages were entirely absent. No brain showed hemolysis of the contents or hyalinization of the walls of vessels. The cerebellum and midbrain were strikingly free from important hemorrhages, such as are observed in cases of trauma.

It may be said, therefore, that small diapedesis hemorrhages, consisting of a few cells limited to the perivascular space, may occur without pathologic signification, and that meningeal and ventricular hemorrhages and small adjacent hemorrhages are frequently produced artificially by removal of the brain.

Group 2. Death Directly Following and Resulting from Trauma (animals B 1, B 2, B 6, B 9 and B 16).—ANIMAL B 1: A 200 day old albino rat was subjected to a single lethal fall from a height of 67 cm., producing bleeding from the nose and clonic convulsions before death. The skull was not fractured. The brain showed superficial meningeal hemorrhages in the frontal lobes and at the base, but no evidence of deep contusion or other gross lesion. The meningeal vessels were widely dilated but showed no petechiae.

Microscopic Pathologic Changes: The whole brain was sectioned serially. The tegmentum showed marked vascular alterations, characterized by hemolytic changes in the contents of veins and petechiae about arterioles. Hemolysis of vessel contents was also noted in the striatum, in the frontal lobes and in the cerebellum. Areas were noted in the pons, medulla and cerebellar white substance which stained poorly and the nerve fibers of which appeared shredded. Diffuse hemorrhagic areas were seen in the cerebellar white substance. The ganglion cells of the midbrain and inferior olive were of normal contours and presented no abnormalities of the nucleus or protoplasm in stained sections. No tears were found in any identified vessels of the parenchyma. The diffuse hemorrhages were presumably due to capillary disintegration or traumatic clefts. In vessels showing hemolysis and diapedesis a shrunken appearance of the endothelial lining was frequently noted.

ANIMAL B 2: A fall from a height of 67 cm. caused the death of a 100 day old albino rat, preceded by convulsions lasting one and a half minutes. Marked pial hemorrhages occurred in the longitudinal fissure between the frontal lobes and at the base surrounding the midbrain.

Microscopic Pathologic Changes: The whole brain was sectioned serially. On the lateral anterior aspect of the midbrain near the third ventricle there was a

large cleft hemorrhage in which were seen polymorphonuclear cells, lymphocytes, cells with large pale oval or round vesicular nuclei resembling oligodendrocytes, transitional cell forms and fibroblasts. A well marked collection of cells resembling oligodendrocytes in the appearance of their nuclei had migrated toward a vessel in the midbrain, the contents of which were hemolyzed and the normal structure destroyed, but in which endothelial (fibroblastic) repair had started (fig. 2). Numerous small hemorrhages were seen in this brain. The subcortical white matter and the basal ganglia, including the amygdaloid nucleus, were the seat of perivascular petechial hemorrhages; a few hemorrhages were also observed in the cortex. Lamellar arrangement of the perivascular blood cells was observed in a

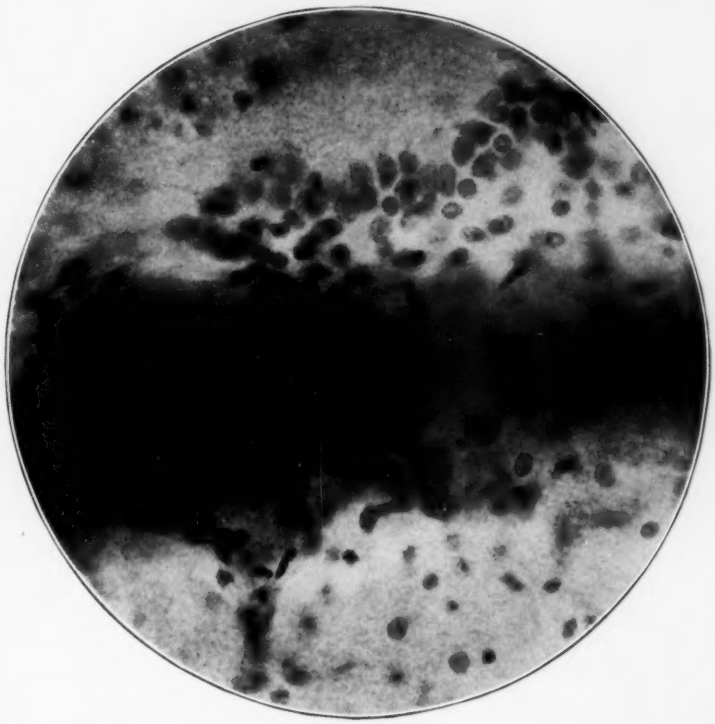

Fig. 2 (animal B 2).—Vessel in the midbrain with hemolyzed contents undergoing fibroblastic repair toward which glia cells are migrating. Hematoxylin and eosin stain.

few vessels with intact but degenerated walls. In the occipital region a hemorrhage followed the course of a blood vessel and its branches. Most vessels showing diapedesis presented some evidence of alteration of the walls. In the larger petechiae traces only of the original degenerated vessel were seen. In some instances there was coalescence of small hemorrhages. Hyalinization of small blood vessels was of frequent occurrence. This was most marked in the interior of the brain, but was also present in the cortex. There were some patchy hemorrhages in the frontal lobes without identifiable vessels. In the lenticular nucleus

strands of nerve fibers had a fibrillated appearance and stained poorly. Injury to this brain consisted of well marked meningeal as well as minute pathologic changes. As in other animals, frank tearing of vessels in the parenchyma was strikingly absent.

Animal B 6: A fall of 62 cm. caused the death in two minutes of a 100 day old albino rat, preceded by bleeding from the nose and convulsions of the hindlegs. Pial hemorrhages were observed on the surface of the cerebrum and cerebellum.

Microscopic Pathologic Changes: The whole brain was sectioned serially. There were scattered perivascular petechial hemorrhages. One vessel with a well

Fig. 3 (animal B 9).—Ring hemorrhages. Hematoxylin and eosin stain.

marked petechial hemorrhage in the left centrum ovale showed an intact endothelial lining. Ball hemorrhages were even more numerous than perivascular petechial hemorrhages, and were seen in the basal ganglia and in the midbrain. The contents of the posterior fossa were relatively free from pathologic change, as was the cerebral cortex. The changes in this brain, therefore, corresponded with those in human material, save for the predominance of ball hemorrhages. There was no evidence of tearing of vessels in the parenchyma.

Animal B 9: A 100 day old albino rat was subjected to a single lethal fall of 67 cm., which caused bleeding from the nose and convulsions, and death in one minute. A thin layer of pial bleeding was observed over various cortical surfaces, with a mesoblastic and fibroblastic cellular reaction.

Microscopic Pathologic Changes: The whole brain was sectioned serially. Perivascular ring and ball hemorrhages were seen in the frontal and temporal lobes and in the corpus striatum and midbrain. This brain was characterized by numerous beginning ring hemorrhages, which were remarkably large in proportion to the size of the vessel (fig. 3). There was a slight but definite clear area about the central disorganized vessel, which could not be identified with certainty as a vein or an arteriole. These vessels were not capillaries. The perivascular petechial type of hemorrhage occurred principally about arterioles. There was no evidence of tearing of vessels in the parenchyma.

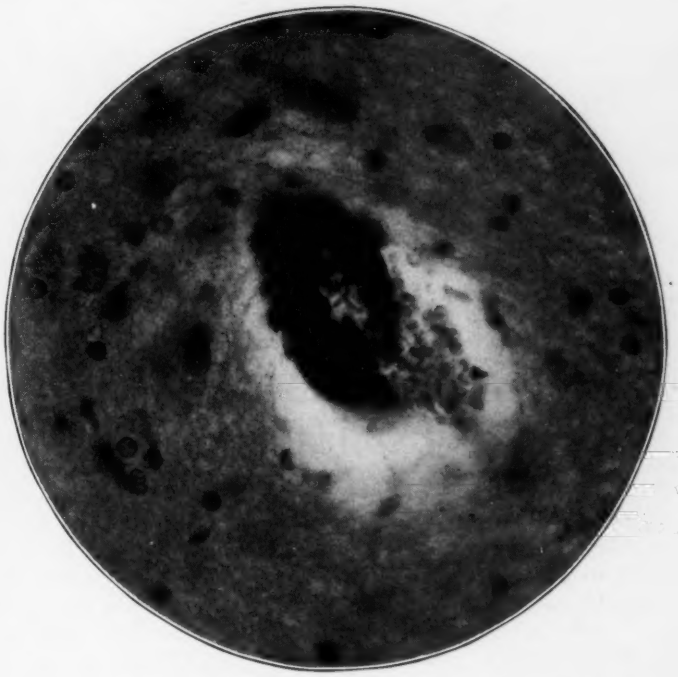

Fig. 4 (animal B 16).—Fresh perivascular petechial hemorrhage about an arteriole in the midbrain, with degeneration of the vessel wall but no evidence of tearing. Hematoxylin and eosin stain.

ANIMAL B 16: A 100 day old albino rat was subjected to two consecutive falls, the second of which was followed by bleeding from the nose and convulsions, and death in one minute. The height of these falls was not recorded. Grossly, the brain showed meningeal hemorrhages in the cerebellar fissures, in the posterior longitudinal fissure and about the quadrigeminal bodies.

Microscopic Pathologic Changes: The whole brain was sectioned serially. Petechial hemorrhages (fig. 4) were observed in the basal ganglia, the medulla, the dentate nucleus and the cerebellar white substance. In the basal ganglia perivascular petechiae were observed about veins as well as arterioles, but more frequently about the latter. There was no evidence of hemorrhage by rhexis within the brain substance. Occasional lysis of red cells was noted in the cerebellar hemorrhages.

As will be seen from the foregoing protocols, the pathologic picture in these severely concussed animal brains showed the constant presence of petechial hemorrhages, without gross lesions to account for death. The presence of pial bleeding was also constant. Other pathologic conditions included hyalinization of vessel walls and lysis of the contents of vessels, shredded appearance and inconstant staining reaction of nerve fibers, degeneration of vessel walls and ball and ring hemorrhages. Less evident were pathologic changes in the ganglion cells. Hemorrhage in the parenchyma by rhexis was not observed.

Group 3. Death at a Definite Interval After Trauma.—Subgroup A. Death Induced After Single or Repeated Traumas in Initial Experiment (animals B 4, B 3, B 8, B 12, B 15, B 10, B 11 and B 17): ANIMAL B 4: A 100 day old albino rat was subjected to a single fall from a height of 60 cm. After this trauma it was slightly less active than before, but resumed normal activity in two minutes. There was no bleeding from orifices about the head. It was killed after an interval of one day. Grossly, save for slight pial hemorrhages, no abnormalities were noted.

Microscopic Pathologic Changes: The whole brain was sectioned serially. No petechial or other hemorrhages were seen in the brain.

ANIMAL B 3: A 100 day old albino rat was subjected to a single sublethal fall of 60 cm. and was momentarily stunned, after which there was paresis of the right hindleg, of short duration. Five minutes after the fall no traumatic effects were noted. Four days later the animal was killed. Pial hemorrhages were present in the occipital poles.

Microscopic Pathologic Changes: The entire brain was sectioned serially. Infiltration of various types of nucleated cells, some with small nuclei and bipolar cytoplasm, was seen in the pia-arachnoid of the convexity. Similar infiltrations in the pia-arachnoid were observed about the frontal poles and in the cortex adjoining the longitudinal fissure. The pia-arachnoid over the cerebellum presented a homogeneous cellular infiltrative appearance. A small hemorrhage was noted in the cerebellar cortex on one side. Some cortical veins presented a wavy appearance of the walls, with degenerated contents. In the thalamus there was occasional evidence of arterial damage, with homogeneous degeneration of the vessel wall and occlusion of the lumen. Infiltrating cells with small to large nuclei and granular protoplasm were seen in the adventitial spaces about these degenerated vessels.

The pial vessels in this brain were greatly dilated, at times having the appearance of hemorrhage. There was some hemorrhage in the aqueduct. Occasionally a few blood cells, but no definite petechial hemorrhages, were seen in the adventitial spaces of blood vessels.

The remarkable feature of this brain was the infiltrative process in the pia and the occasional degenerative process in the arteries in the interior of the brain. The fresh hemorrhages were of the type produced by removal of the brain. There was no tearing of vessels in the parenchyma.

ANIMAL B 8: A 100 day old albino rat was traumatized by a single fall of 60 cm.; it was stunned for ninety seconds and then showed weakness in the hindlegs, with recovery in three minutes. It was killed twenty-six days after the trauma. No gross lesions were observed.

Microscopic Pathologic Changes: Serial sections were made of the whole brain. Considerable connective tissue thickening and infiltration of various areas in the pia-arachnoid were present, particularly in the frontal and occipital poles, where there was a heavy infiltration of mesothelial cells and fibroblasts. No perivascular petechial hemorrhages were observed, but some hemorrhages of removal type were seen at the frontal poles. In the corpus striatum, especially in the lenticular nucleus, there was evidence of parenchymatous involvement in probable relationship to damaged vessels; this is illustrated (fig. 5) by a small area in the lenticular nucleus showing infiltration of glia cells and fibroblasts. There were many small capillaries in this scar formation.

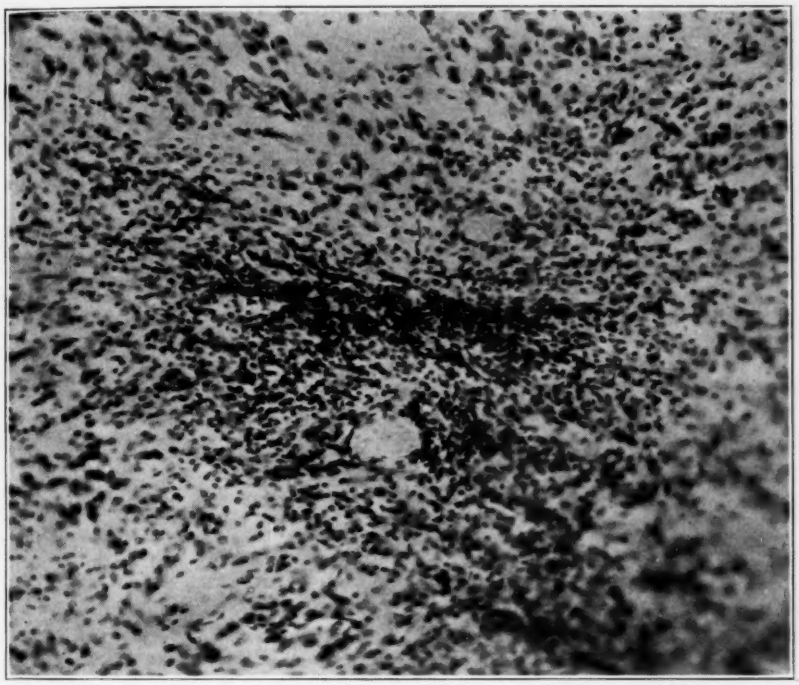

Fig. 5 (animal B 8).—Glial scar in the lenticular nucleus. Hematoxylin and eosin stain.

ANIMAL B 12: A 100 day old albino rat was subjected to three falls of 60 cm., at recovery intervals. After the first fall the animal ran in circles; after the second it was stunned and remained quiet for approximately one minute; after the third it was stunned, but moved when stimulated. The right front leg was weak; the animal moved about spontaneously in three minutes after the third fall. It was killed after an interval of twenty-six days. No gross changes were noted in the brain.

Microscopic Pathologic Changes: Serial sections were made of the whole brain.

Section 20. There were cellular infiltrations, mostly with mesothelial cells and fibroblasts, in the pia-arachnoid. These were particularly marked about the posterior aspect of the brain.

Section 27. Dilatation of veins was noted throughout, especially in the cerebellum. No hemorrhage was seen in the brain substance.

Section 111. There were extensive meningeal hemorrhages of the removal type about the medulla.

Section 151. A few small arteries in the corpus striatum were greatly thickened; this may have been due to previous hemorrhage, although there was no definite evidence of old hemorrhage. Neither was there any trace of new hemorrhage in the brain substance.

Section 170. In the midbrain there was an artery with heavy infiltrations of about eight layers of cells in and about the wall. A study of these cells with the hematoxylin-eosin stain showed some fibroblastic types, but no definite lymphocytes or phagocytes. The nature of the majority of the infiltrating cells around the vessel was not definitely determined with this stain. The shape and size of the nuclei varied. Small nuclei were mostly round or oblong, but some were curved. These small nuclei were scattered around the vessel for some distance in the brain tissue. By the Kanzler silver method the cells were determined to be of microglial and oligodendroglial type. The gold stain was not satisfactory, but the morphologic character of the nuclei of medium size, particularly those showing indentations, suggested astrocytes.

Sections 180-190-200 (midbrain). The lowest of these sections showed well marked removal hemorrhages, which extended, but to a much more limited degree, to the uppermost section. Red blood cells were seen in the tissues about a group of blood vessels, for the most part with thickened walls, some of which showed hyaline degeneration of the adventitia. In various portions of these sections areas of gliosis were noted, indicating parenchymatous defects of old traumatic lesions.

Summary. This brain was subjected to three successive injuries and may therefore be classified as more severely traumatized than that of the preceding animal. The signs of parenchymatous gliosis and vascular degeneration were fairly well marked.

Animal B 15: A 100 day old albino rat was subjected to three successive traumas by falls of 27 cm. The animal showed no effects after the first two traumas; after the third it was stunned, bled from orifices about the head and had a generalized convulsion. Two minutes after the last trauma the animal moved on being prodded, but showed general weakness, most marked in the left extremities. It was killed twenty-eight days after trauma. Grossly, the brain showed nothing remarkable.

Microscopic Pathologic Changes: The whole brain was sectioned serially. The veins in the cerebral hemispheres and the cerebellum were dilated and many of them thrombosed. The pia-arachnoid was thickened and infiltrated with cells in many places. The walls of a deep-seated cortical vein anterior to the nucleus amygdalae were degenerated and surrounded by a small, but well defined, perivascular petechial hemorrhage. Removal hemorrhages were observed superficially in the cerebellar white substance and in the meninges, midbrain and pons.

A noteworthy feature of this brain was thickening of the arteries, which was particularly marked in the midbrain, lenticular nucleus, thalamus and cerebellum. A number of these thickened blood vessels showed thromboses. In the pons there was a circumscribed area of thickened arterioles which were thrombosed and veins which showed laking of contents. There was no definite trace of old hemorrhage in this brain, and only one vessel, the vein mentioned previously, showed the results of trauma in late diapedesis.

ANIMAL B 10: A 100 day old albino rat was subjected to a fall of 60 cm., which caused it to bleed slightly from the nose and to remain stunned for one minute. It was killed thirty days after the trauma. No gross changes were noted in the brain.

Microscopic Pathologic Changes: Serial sections of the whole brain were made. Section 55. The pia-arachnoid showed hyperplastic changes, especially at the frontal pole and around the posterior aspect of the brain. There were a great increase of fibrous connective tissue and a heavy cellular infiltration in the pia-arachnoid. The infiltrating cells consisted of fibroblasts, mesothelial cells and lymphocytes. Meningeal hemorrhages of removal type were seen around the midbrain. No hemorrhage was noted in the brain substance proper.

Section 95. In the amygdaloid nucleus there was an area of cellular infiltration, which appeared to be in the region of an old hemorrhage. The infiltrating cells were fibroblasts and neuroglia cells. Fibroblasts could be identified by their elongated nuclei. The microglia cells were characterized by small round and somewhat elongated nuclei and the astrocytes by relatively larger nuclei.

ANIMAL B 11: A 100 day old albino rat was subjected to a single fall of 60 cm. and was stunned for ninety seconds, not recovering much activity until after three minutes. It was killed fifty-five days after trauma. Adhesions between the dura and the pia-arachnoid were observed at the vertex, which showed reddish discoloration. One half of the brain was cut in the sagittal plane and prepared for section in the usual manner; these sections were numbered from the lateral aspect to the median line.

Microscopic Pathologic Changes: Section 60. At the junction of the pons and the medulla there was cellular infiltration, marked about veins. This infiltration was not in the form of cuffing, but appeared to be clustered about the vessel.

Section 121. In the medulla cellular infiltrations were present along the vessel walls. Most of the infiltrating cells were fibroblasts, in addition to which were many cells with round and oval nuclei. The pia-arachnoid showed slight thickening and some cellular infiltrations, especially at the frontal and posterior aspects of the brain.

ANIMAL B 17: A 100 day old albino rat was subjected to five successive falls of 27 cm., without appreciable effect. After the sixth trauma it was stunned for one minute; after the seventh trauma it suffered generalized convulsions, but showed no bleeding from orifices of the head. It remained stunned for five minutes, after which it was lethargic. The animal was killed fifty-two days after trauma. Grossly, the brain showed no superficial pathologic change, save marked congestion of the superficial vessels about the longitudinal fissure.

Microscopic Pathologic Changes: Serial sections of the left hemisphere were made.

Section 85. Deep in the frontal lobe there was a small area of cellular infiltration. This area seemed to be the site of an old hemorrhage in the process of repair. In one corner of this area was a persisting blood vessel, which was surrounded by heavy cellular infiltration. From the appearance of the nuclei the infiltrating cells seemed to be predominantly astrocytes. Scattered scarring of the pia-arachnoid was observed.

Section. 115. This section showed a lesion in the midbrain similar to that seen in section 85. The arrangement of the cellular infiltration here simulated that of a ring hemorrhage.

Subgroup B. Death Induced After Repeated Traumas on Successive Days (animals B 13 and B 24): ANIMAL B 13: A 100 day old albino rat was subjected to five successive falls of 27 cm. in the initial experiment, with no evidence of stunning. Twelve days later the animal was again traumatized. It bled from a laceration above the right eye and was stunned for three minutes, moving infrequently. It was killed forty-three days after the last trauma. There was congestion of pial vesesls, but no evidence of gross injury to the brain.

Microscopic Pathologic Changes: The brain was fixed in a solution of formaldehyde, and after hardening was divided into halves. From the left hemisphere pyroxylin serial sections were cut; from the right hemisphere frozen sections were made, which were stained with scarlet red for evidence of myelin degeneration, with negative results. The pia-arachnoid showed marked cellular infiltration on the posterior aspect of the brain. The pial vessels were dilated. There was no trace of old injury in this brain, but perivascular removal hemorrhages were seen in the brain stem and the cerebellar white matter.

ANIMAL B 24: A 100 day old albino rat, weighing 260 Gm., received six single traumas during a period of seven days; the height of the falls was 27 cm. No effect was noted after the first two traumas, on successive days. The animal was again traumatized by a fall from a similar height after a free interval of one day, after which there was a slight hemorrhage of the right eye. The subsequent daily traumas produced no apparent effect, save for profuse bleeding from the nose and some hemorrhage in the right eye after the last trauma. This animal showed no abnormalities up to the time of death, two hundred and eighty-two days after the last trauma. Its weight gradually increased, registering 470 Gm. at death. On removal the brain showed no abnormality. The hemispheres were divided; one hemisphere was fixed in a 10 per cent solution of formaldehyde, the other in a solution of formobromide.

Microscopic Pathologic Changes: The formaldehyde-fixed hemisphere was cut in serial sections and stained in the usual manner. Occasional removal hemorrhages of fresh cells were noted in the meninges, but there was no perivascular cuffing or evidence of gliosis in the interior of the brain. In section 15 the pia-arachnoid over the frontal pole showed a patch of heavy cellular infiltration. Mesothelial cells and fibroblasts were predominant. There was nothing unusual in the sections, therefore, save the focal meningeal reaction already noted.

SERIES TWO

Group 1.—Death induced at a definite interval after single or repeated traumas in initial experiment: 4 animals.

Group 2.—Death induced after repeated traumas on successive days: 1 animal.

In this series the interval between the last trauma and death was approximately two months. One hemisphere only was sectioned serially for routine staining, and the sections were numbered from the base to the vertex. Selective staining for glia was done in all cases.

Group 1. Death Induced After Single Trauma or Repeated Traumas in Initial Experiment (animals C 20, C 35, C 41 and C 43).—ANIMAL C 20: A 100 day old albino rat was traumatized by a single fall of 50 cm., which resulted in clonic convulsions followed by a period of unconsciousness. The animal did not move spontaneously until five minutes after the fall. Transient paresis was noted on the right side. The animal was killed seventy days after the trauma. A pinpoint

area of dark brownish pigmentation was noted at the posterior surface of the medulla; otherwise the brain appeared normal.

Microscopic Pathologic Changes (left hemisphere): Section 11: The meninges were thickened.

Section 25. A centrally located thrombosed artery in the corpus striatum showed evidence of a fibroblastic reparative process.

Section 26. A fresh meningeal hemorrhage of removal type was noted. A light area about a thickened arteriole may have represented a parenchymatous defect.

Section 36. A small arteriole in the subthalamic region showed pathologic alterations in an irregular and sacculated lumen (fig. 6). Extensive cellular infil-

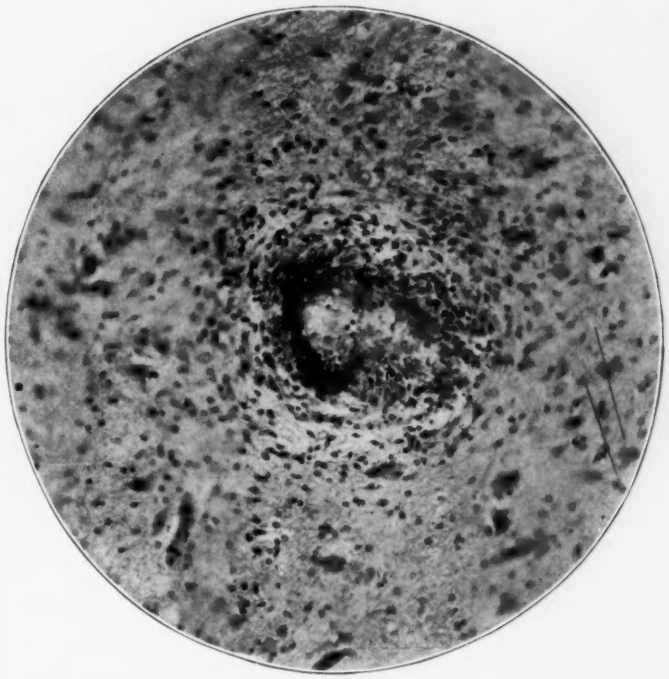

Fig. 6 (animal C 20).—Aneurysmal (saccular) deformity of an arteriole in the subthalamic region. Hematoxylin and eosin stain.

tration about this vessel extended well into the parenchyma. Under high magnification, normal red cells were seen in the lumen but not outside the wall of the vessel. The wall showed hyaline degeneration, especially in the region of the sacculated aneurysmal portion. The wall itself was infiltrated with fibroblasts, which were abundant in the periadventitial space. In this space a few gitter cells, as well as microglia and occasional oligodendroglia cells, were observed. In the adjoining parenchyma an increase of astrocytic cells was observed. This vessel was traced from section 31 to section 45.

Section 55. A removal hemorrhage was noted in the interpeduncular space.

Section 105. A small vein in the frontal lobe near the longitudinal fissure appeared to be the site of an old petechial hemorrhage. The vein was sectioned obliquely. In the wall were red blood cells, surrounded by homogeneous material, probably serum. The wall was thin and literally covered with infiltrating cells. The tissue surrounding this vein was vacuolated and infiltrated with cells. The nature of these cells was difficult to determine. From their size and shape most of them seemed to be astrocytes. Oligodendroglia nuclei could be recognized by their regular round or oval outlines. Microglia cells seemed to be rare; however, a few gitter cells were noted.

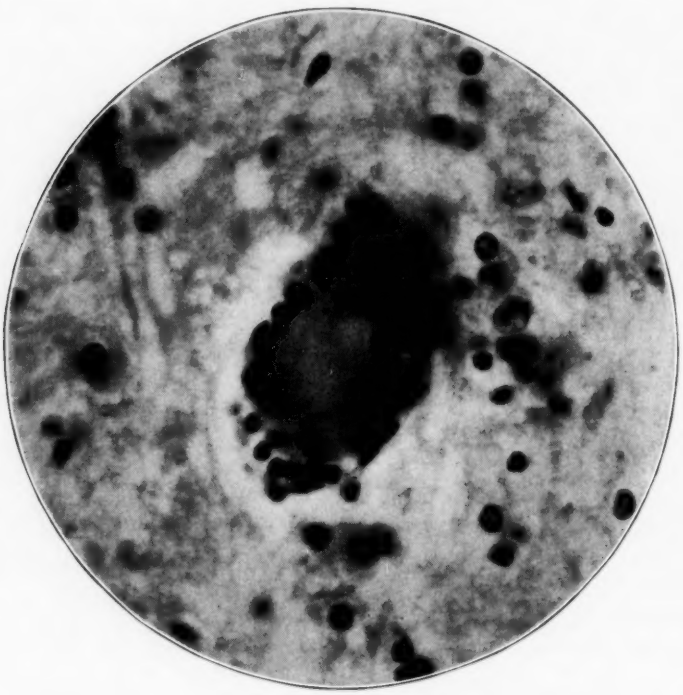

Fig. 7 (animal C 35).—Cuffing of microglia about a tegmental vein. Hematoxylin and eosin stain.

Section 120. In the tegmentum, near the midline, was observed an accumulation of cells, evidently about an obliterated blood vessel, which were similar to those already mentioned.

Section 135. Infiltration extended into the parenchyma of the parietal cortex from the meninges. The nuclei of the infiltrating cells were astrocytic in type.

Section 155. A slight meningeal hemorrhage was noted.

Section 185. A perivascular hemorrhage of removal type was seen in the corpus striatum near the internal capsule.

Summary. Definite vascular pathologic changes in this case were limited to four vessels, one in the corpus striatum, one in the subthalamic region, one in the frontal lobe near the longitudinal fissure and one in the tegmentum. They showed

essentially the same picture, namely, cellular gliosis about and within the wall of a damaged blood vessel, presumably the site of a pathologic perivascular concussion hemorrhage. The gliosis was confirmed by silver impregnation (Kanzler), astrocytes and microglia predominating.

ANIMAL C 35: A 100 day old albino rat was stunned by a single trauma, a fall of 50 cm. The following day a similar fall caused momentary loss of consciousness but no convulsions. A few minutes later a more effective fall resulted in clonic convulsions, unconsciousness for ten minutes and loss of the corneal reflex. There was transient paresis of both hindlegs. The animal was killed sixty

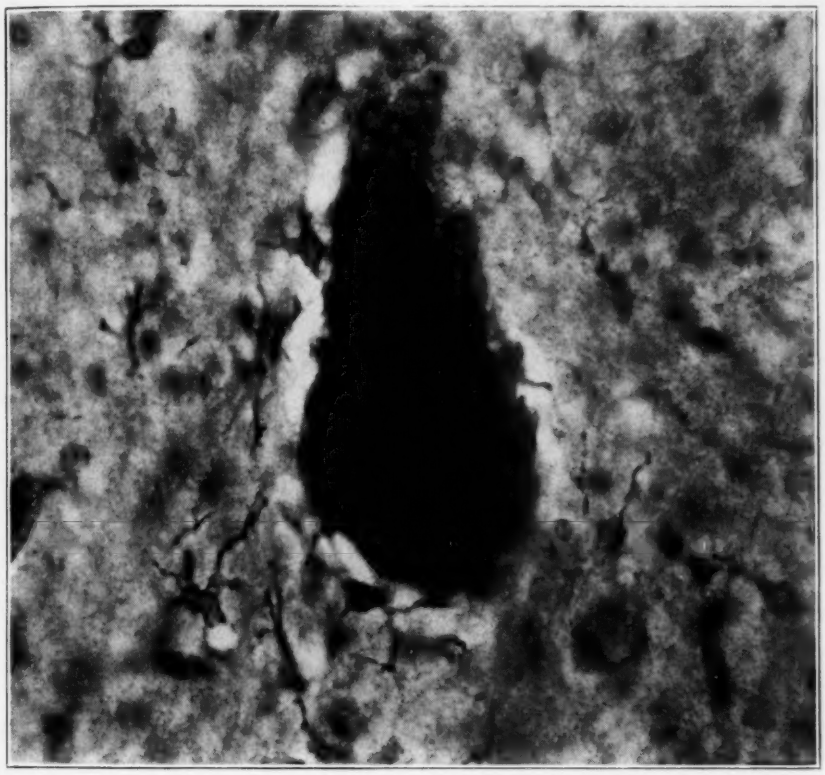

Fig. 8 (animal C 35).—Section adjoining that shown in figure 7. The predominating perivascular cell type is microglial. Kanzler stain; × 700.

days after the last trauma. Grossly, the brain showed brownish pigmentation in the posterior end of the longitudinal fissure.

Microscopic Pathologic Changes (left hemisphere): Section 51. With the hematoxylin-eosin stain cellular infiltration, consisting of deeply stained mononuclear cells (fig. 7), was noted about a small vein in the tegmentum. The Kanzler stain proved them to be microglia cells in the early cicatricial stage (fig. 8).

Section 70. A collection of cells was seen in the frontal cortex, which under low magnification resembled a tubercle with central caseous necrosis. Under greater

magnification the central portion was seen to be occupied by homogeneous material, in which a few scattered cells were embedded. At the border of this area was a zone of cells with oval or elongated nuclei. No giant cells were noted. This area was traced to section 106.

Section 110. A meningeal hemorrhage of removal type was noted, which could be followed to section 160.

Summary. In addition to marked dilatation of veins and scattered meningeal hemorrhages of removal type, there was a tegmental vessel showing marked cuffing of microglia cells. The general appearance of the brain stem suggested that the tegmentum was the seat of a parenchymatous degenerative process; this of course could not be proved without special staining.

Fig. 9 (animal C 41).—Temporal cortex. Fibroblastic and astrocytic scar formation replacing a destroyed vessel. Hematoxylin and eosin stain.

Animal C 41: A 100 day old albino rat was traumatized once by a fall from a height of 50 cm. The fall resulted in flexion of all limbs, followed by extreme rigidity of the body and clonic convulsions. The animal did not respond to external stimuli for four minutes. The corneal reflex did not return for over two minutes. The animal was killed seventy days later. There was a small area of brownish pigmentation in the posterior extremity of the longitudinal fissure.

Microscopic Pathologic Changes (Right Hemisphere): Section 11. In the temporal cortex concentrically arranged fibroblastic fibers were interspersed among cells which by the Kanzler stain were shown to be astrocytic (fig. 9). This scar tissue evidently replaced a destroyed vessel.

Section 111. Meningeal scarring was noted on the lateral aspect of the medulla.

Section 130. Meningeal scarring was seen in the frontal pole.

Section 166. A small area of cellular infiltration in the thalamic region appeared to consist chiefly of astrocytes replacing a destroyed vessel.

Sections 185 and 195. Cellular accumulations were seen in the subthalamus and thalamus.

Section 201. Gliosis in the midline of the medulla showed cellular characteristics similar to those in the lesions in the preceding sections and the same tendency to a whorled or laminated appearance, suggesting the outline of an obliterated vessel.

Fig. 10 (animal C 37).—Perivascular hemorrhage about a vein in the subcortical white matter of the temporal lobe. The blood within the vessel is fresh; that outside the vessel is old. Hematoxylin and eosin stain.

Summary. This brain was characterized by the greatest number of areas of gliosis in the series. They presumably replaced damaged vessels. All of these areas occurred in the deeper portions of the brain, lesions in the subthalamus and medulla being especially frequent.

ANIMAL C 43: A single fall of 50 cm. caused mild clonic convulsions and loss of consciousness in a 100 day old albino rat. The corneal reflex was lost for a short time. The first voluntary movement was made four minutes after trauma. The animal was killed sixty days later. Grossly, nothing abnormal was noted in the brain.

Microscopic Pathologic Changes (right hemisphere): Sections 65-66. Definite scarring with evidence of fresh removal hemorrhages was seen at the surface of the temporal lobe. The underlying cortex appeared normal.

Section 110. A number of vessels showed laking of contents.

Summary. This brain was practically normal, except for evidence of meningeal scarring, apparently due to reparation of traumatic hemorrhage.

Group 2. Death Induced After Repeated Traumas on Successive Days.—Animal C 37: An initial fall of 50 cm. did not result in marked immediate effects on a 100 day old albino rat. The following day, however, the left pupil was observed to be larger than the right and the animal appeared lethargic. On this day the animal was subjected to two more traumas by falls of 50 cm. The first one stunned it, and the second resulted in marked clonic convulsions of both trunk and limbs, followed by a period of unconsciousness. The animal was killed sixty days later. Grossly, dark brownish pigmentation was noted in the fissures between the left frontal lobe and the olfactory bulb.

Microscopic Pathologic Changes (Left Hemisphere): Section 10. A fresh hemorrhage, probably of removal type, was seen in the nerve fibers in the region of the quadrigeminal bodies. Suspicious evidence of disorganization of a capillary wall and laking of vessel contents were noted in the temporal cortex.

Section 55. A well marked perivascular petechial hemorrhage was observed in the subcortical white matter of the temporal lobe about a vein, the walls of which were well defined and intact (fig. 10). The blood within the vessel was fresh; that outside was old. Definite thinning of the parenchyma surrounding this vessel was seen for a considerable distance.

Section 75. Parenchymatous removal hemorrhages were noted near the cut surface and the ventricular wall.

Section 136. Another cleft hemorrhage of removal type was present on the lateral aspects of the frontal lobe near the frontal pole.

Summary. Numerous small removal hemorrhages were observed near the surface and near the ventricles. One large pathologic perivascular petechial hemorrhage was present in the subcortical white matter of the temporal lobe. This brain showed no vascular pathologic change other than the one perivascular petechia. A Kanzler stain was not successful in this preparation.

The second series, therefore, shows the usual picture of meningeal scarring, vascular degeneration and parenchymal gliosis.

COMMENT

Traumatic petechial hemorrhages of the brain have long been recognized in association with severe injury to the head. They have been particularly investigated by Jakob [2] in animal experimentation and by Ricker [3] in studies of the vasomotor system. The literature on the

2. Jakob, A.: Experimentelle Untersuchungen über die traumatischen Schädigungen des Zentralnervensystems (mit besonderer Berücksichtigung der Commotio cerebri und Kommotionsneurose), in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1913, vol. 5, p. 182.

3. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

subject has been reviewed in previous articles by us.[4] The present article has attempted a critical appraisal of the significance of these hemorrhages, especially after a considerable period of survival, and their role in the more subtle changes produced by trauma of the brain.

Traumatic perivascular petechial hemorrhages of the brain, similar to those found in severely traumatized human brains, have been reproduced by us in fatally injured white rats, namely, perivascular diapedesis and ring and ball hemorrhages. The simple perivascular type was represented by an appreciable accumulation of red cells in the Virchow-His space, which was generally considerably dilated. The distribution of cells in this space was in some instances uniform, in others localized. The larger type of petechiae showed a tendency to invade the parenchyma. Ring hemorrhages, we believe, are only an advanced stage of the more extensive perivascular type, the ring of blood cells representing the parenchymatous infiltration and the clear space the perivascular fluid attaining its original channel and clearing this space of red cells. In the center of the clear space some detritus was generally observed, the remains of a small disorganized vessel. The ball hemorrhages are in all probability an offset cut through the hemorrhagic portion. In all the 5 cases in which death directly followed trauma petechial hemorrhages were noted. These were associated with the smaller parenchymal arterioles and venules. In animals B 1 and B 16 they were more frequent about arterioles. Capillary diapedesis is assumed, rather than demonstrated, because of the difficulty of defining the delicate and obscured vessel wall.

As in human brains, the evidence points to vascular concussion effects in the production of petechiae, namely, vasodilatation, prestasis and stasis, anoxemia, permeability of the vessel wall and diapedesis. This pathologic picture was particularly evident in the deeper cerebral structures, as was also found to be the case in human brains; however, as the centrum ovale in the white rat is relatively small, the deeper layer of the cortex was at times involved, an infrequent observation in human brains. A wide distribution of these petechiae was evident in examining the protocols; they were observed in the substance of both the cerebral and the cerebellar hemispheres, as well as in the basal ganglia and the brain stem. It was not evident that they predominated about the central channels of the fluid pathways, such as the walls of the aqueduct and medulla, as suggested by Duret [5] in his theory of fluid transmission of force. However, this question might be more definitely settled by using

4. Schaller, W. F.: After-Effects of Head Injury, J. A. M. A. **113**:1779 (Nov. 11) 1939. Schaller, Tamaki and Newman.[1]

5. Duret, H.: Notes sur la pathologie des traumatismes cérébraux, Gaz. méd. de Paris **6**:598, 612 and 624, 1877.

serial horizontal, rather than longitudinal, sections, as was practiced here. No gross defects, such as tearing of the vessel walls, were demonstrated as a cause of hemorrhages of this type in complete serial sections. Death apparently was not due to gross pathologic changes, but to severe irreversible concussion effects. The so-called vacuolation was found to be an artefact, produced by formaldehyde fixation. By special staining, vacuolated spaces were found to be empty and not due to the presence of swollen oligodendrocytes.

Other pathologic changes noted in the animals which died directly after injury were hyalinization and degenerative changes in vessel walls, hemolysis of vessel contents and cellular infiltrations of glia and mesoblastic elements about damaged vessels and the meninges. These infiltrative processes would be inexplicable, save for the slight but definite interval between trauma and death in which vital processes were still operative in an animal whose metabolic rate is thirty times that of man. Pial bleeding was frequently observed as a superficial contusion effect.

In animals killed an appreciable interval after concussion, fresh petechiae were infrequently seen (animals B 15 and C 37), and then generally in relation to obviously damaged vessels (animal B 15). In several of the animals (B 17 and C 35) a glial cuffing around vessels represented replacement of a former perivascular petechial hemorrhage. One brain (animal B 13) showed many small vessels in which the adventitial space contained a small number of fresh red blood cells. Careful study of this brain by comparison with normal controls identified these perivascular accumulations as "removal hemorrhages." The uniform appearance of the red cells, lack of fixed tissue reaction and absence of damage to the vessel walls further identified the picture as an artefact. It is quite likely, also, that the apparently fresh meningeal bleeding in intact vessels in the animals killed at an interval after trauma is largely, if not entirely, due to the same mechanism. Study of the normal controls also established "shredding" as an artefact. The finding of thickened vessels in one of the control series (animal C 3) established the fact that such a condition in the traumatized animals is not necessarily due to trauma. When found in traumatized animals (B 3, B 12, B 15 and C 20) these vessels were at times the seat of thromboses (animal B 15). Thromboses were frequently noted; a typical example was the central thrombosis of the ring hemorrhages (fig. 3).

Degeneration of vessels in animals killed after an interval was a marked feature of the pathologic picture, and in general may be said to follow the same localization as the petechiae. Among the histologic changes observed were capillary disintegration (animal C 37), cellular infiltration of the walls of smaller vessels (animal C 35), hyaline degeneration of the walls and sacculated aneurysmal deformation (animal C 20). Hyaline changes in the adventitia of thickened vessels were

noted (animal B 12). Areas of parenchymatous gliosis were found in animals B 8, B 12, B 10, B 11, B 17, C 20, C 35 and C 41. A tendency to a whorled or laminated appearance frequently suggested the outline of a degenerated vessel with organization of the unresolved petechial hemorrhage. We may therefore trace the sequence from unresolved petechiae to manifest changes in the vessel wall, disintegration and gliosis. This raises the question of the principal or primary concussion effect, namely, whether it involves the circulatory system, the ganglion cells or the conduction fibers. It is obvious that this question can be decided only by an intensive study of all these tissues and an evaluation of their relative involvement. Some light may be shed on this problem by indirect, as well as direct, evidence, namely, by the location and character of replacement gliosis. In our animals this has appeared to be more directly related to damaged vessels than to damaged nerve cells or myelin. We have not seen any evidence in our material of the myelin necrosis emphasized by Schmaus as occurring in the spinal cord or by Kocher as present in the brain. Furthermore, the lack of gliosis at a distance from pathologic changes in the vessels and the absence of cells of scavenger and gemästete reaction type are against the theory of primary myelin degeneration. No instances of red softening were encountered. The mechanism of injury in our experiments differs from that in the Schmaus experiments, which may account for the difference in the pathologic picture described by this author.[6] One of us (Tamaki) has been occupied with a study of primary traumatic myelin alteration in material from the foregoing experiments, and has specially stained sections by the Courville modification of the Pal-Weigert stain, by the Marchi technic and with scarlet red; sections are now being studied with polarized light. None of these methods as yet has produced satisfactory or conclusive results; the difficulty in demonstration of myelin degeneration in the brain as compared with that in the cord or the peripheral nerves is well known to every neuropathologist.

It may be asserted from the evidence in our experiments that severe and irreversible concussion effects cause vascular damage in the brain, with definite tendency to reparation and self limitation; although there may be a chronic circulatory defect in the function of a given vessel, there is no tendency to progressive pathologic involvement of the vascular system. This is shown in the detailed histologic study of the brains of animals killed at an interval after trauma, particularly in the two month series. In no case in our series was there a picture of late softening or apoplexy; however, in 1 case (C 20) a defective, but still functioning, vessel may have represented such a possibility. After

6. Schmaus, H.: Beiträge sur pathologischen Anatomie der Rückenmarkserschütterung, Virchows Arch. f. path. Anat. **122**:470, 1890.

recovery from initial concussion effects, the surviving animals, 15 in number, appeared as a whole to thrive and to show no obvious effects of concussion. From the point of view also of the histologic picture of the brains as a whole, they showed far less pathologic change than one is accustomed to see, for example, as a result of severe degenerative or inflammatory diseases of the brain.

Extremes of pathologic change may be represented in cases of recovery, on the one hand, by slight or no pathologic alterations in animal B 4 (one fall of 60 cm.), in animals B 13 and B 24 (repeated falls of 27 cm.) and in animal C 43 (one fall of 50 cm.), in which only pathologic alterations in the pia-arachnoid were evident, and, on the other, by marked changes in the brain in animal B 12 (three falls of 60 cm. at recovery intervals) and in animal C 41 (one fall of 50 cm.).

It may be said generally of our experiments that the less the clinical effects of concussion the less the demonstrable pathologic changes in the brain (animals B 4 and B 24). Whereas pronounced traumatic effects were followed as a rule by well defined parenchymatous changes, this was not always the case (animals B 13 and C 43).

Animals B 15, B 17, B 13 and B 24 were subjected to repeated concussions by falls from moderate heights in order to study the effects of summation of trauma, as has been alleged to occur in cases of "punch drunk." Of these animals, all save B 24 appeared to be more susceptible to repeated traumas. The character and site of the pathologic lesions, however, were the same.

It is obviously impossible exactly to compare the effects of concussion trauma to the brain in man and those in the white rat, because of the variables incidental to resistance of the species, height of fall, acceleration of fall, comparative weight of the animal, anatomic differences in skull and brain structure and precise evaluation of post-traumatic symptoms. The most evident lesions, however, are the same and may be defined as vascular damage due to irreversible concussion effects.

CONCLUSIONS

By a special device white rats were subjected to a propulsion impact injury to the head, similar to the mechanism of head injuries in man frequently occurring in automobile accidents.

The severity of the trauma was regulated by the height of the fall, and effects of single, as well as repeated, traumas directly after the trauma and at varying intervals following the last trauma were noted.

By the methods employed by us, histologic alterations in the brain produced by concussion trauma were referred chiefly to the vascular apparatus.

Traumatic petechiae by diapedesis, thrombotic and hyaline vascular changes and hemolysis were reproduced in the concussed brain of the albino rat which were in all respects similar to those observed in concussed human brains.

These changes were in the main proportionate to the severity of the trauma, but a considerable variation of effect was noted in different animals.

The vascular pathologic lesions described are due to specific concussion effects, and differ from contusion, laceration and tearing; they are the result of vascular dilatation, stasis and anoxemia. Reversible effects of concussion were demonstrated by the resorption of perivascular petechiae constantly found in recently traumatized animals, but rarely observed in the animal killed at an interval after trauma. Irreversible effects may be followed by demonstrable organic lesions.

The pathologic alterations due to irreversible concussion effects involving the blood vessels and the surrounding parenchyma were found to have a definite tendency to reparation by final obliteration of the damaged vessel and replacement gliosis. There was no instance of a large secondary hemorrhagic or softening process, and no tendency to progression of vascular pathologic lesions.

ARSENIC AS A POSSIBLE CAUSE OF SUBACUTE ENCEPHALOMYELITIS

CORRELATION OF CHEMICAL, CLINICAL AND HISTOLOGIC OBSERVATIONS

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The present study resulted from the observation that the clinical course in cases of subacute, fatal encephalomyelitis frequently seems attributable to the continuous action of some toxic agent. Considerable amounts of arsenic were found in the brain in most such instances in which that tissue was available. It is proposed in this study to consider the possible significance of these facts by correlating the clinical, pathologic and chemical features in cases of this type.

REVIEW OF LITERATURE

Under modern conditions, there is the growing likelihood that large numbers of persons exposed continuously to arsenic from a multitude of legitimate everyday sources may be slowly poisoned through its cumulative effects.[1] In a complicated and irresponsible society, the detection and control of intake of arsenic are perhaps impossible at present.[2] Also it is probably impossible to remove a patient from all contacts with arsenic.[1b]

From the Section on Pathologic Anatomy, the Mayo Clinic (Dr. Kernohan).

Read before the meeting of the American Association of Neuropathologists at Rye, N. Y., June 6, 1940.

Abridgment of thesis submitted by Dr. Arthur D. Ecker to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements of the degree of Doctor of Philosophy in Neurology.

1. (*a*) Hanzlik, P. J.: Health Hazards of Chemo-Enemies in Contaminated Foods, Scient. Monthly **44**:435-439 (May) 1937. (*b*) Cannon, A. B.: Chronic Arsenical Poisoning: Symptoms and Sources, New York State J. Med. **36**:219-241 (Feb. 15) 1936. (*c*) Myers, C. N., and Throne, B.: The Relation of Arsenic to Public Health, ibid. **29**:871-874 (July 15) 1929. (*d*) Heffter, cited by Leibowitz.[8a]

2. Sheldon, W. D.; Doyle, J. B., and Osterberg, A. E.: Neuritis from Arsenic and Lead: The Significance of Chemical Studies in Diagnosis, Arch. Neurol. & Psychiat. **27**:322-332 (Feb.) 1932.

A review of the European [3] and American [4] literature on arsenism shows that cerebral signs not only are present but also are often the leading clinical features of the disease. These symptoms are primarily headache and physical and mental fatigue. This clinical picture is not unlike that of neurasthenia.[3a] However, dizziness, restlessness, excitability and mental dulness may be present. Arsenical poisoning, therefore, is manifested frequently by cerebral symptoms. Unfortunately, in none of the preceding reports of such cases were microscopic studies of the brain reported.

For more than one hundred years [5] there has been continual dispute as to whether or not arsenic is a normal constituent of the human body. However, the opinion of the majority of modern toxicologists [6] has been epitomized by Kunkel,[7] who stated that the so-called normal

3. (*a*) Petrén, K.: Les différentes formes de l'arsénicisme, Paris, Masson & Cie, 1926. (*b*) Bumke, O.: Die exogenen Vergiftungen des Nervensystems, in Lewandowsky, M.: Handbuch der Neurologie: Spezielle Neurologie II, Berlin, Julius Springer, 1912, vol. 3, p. 1070. (*c*) Leschke, E.: Fortschritte in der Erkenntnis und Behandlung der wichtigsten Vergiftung, München. med. Wchnschr. **1**:57-62 (Jan. 8) 1932. (*d*) Bumke, O., and Krapf, E.: Exogene Vergiftungen des Nervensystems. Vergiftungen durch anorganische und organische sowie durch pflanzliche, tierische und bakterielle Gifte, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, pp. 721-727. (*e*) Balthazard, V.: Arsenic (Poisoning by); (Arsenicism), in Occupation and Health, Geneva, Switzerland, International Labour Office, 1930, vol. 1, pp. 159-168.

4. Taylor, A. S.: On Poisons in Relation to Medical Jurisprudence and Medicine, ed. 2, Philadelphia, Blanchard & Lea, 1859, pp. 330-331. Putnam, J. J.: On Chronic Arsenic Poisoning, Especially from Wall-Paper, Based on the Analysis of Twenty-Five Cases in Which Arsenic Was Found in the Urine, Boston M. & S. J. **120**:235-237 (March 7) 1889. Myers, C. E.; Throne, B.; Gustafson, F., and Kingsbury, J.: Significance and Danger of Spray Residue, Indust. & Engin. Chem. **25**:624-626 (June) 1933. Cornwall, L. H.: Some Neurological Syndromes Produced by Arsenic and Lead, Bull. Neurol. Inst. New York **5**:28-36 (Aug.) 1936.

5. (*a*) Couerbe, cited by Brahme.[10g] (*b*) Orfila, cited by Boos and Werby.[6a] (*c*) Gautier, A.: L'arsenic existe-t-il dans tous les tissue de l'économie animale. Compt. rend. Soc. de biol. **55**:1076, 1903; (*d*) Arsenik kommt normaler Weise im thierischen Organismus vor und ist besonders in den ektodermalen Organen localisirt, Ztschr. f. physiol. Chem. **36**:391-397 (Oct. 1) 1902; (*e*) cited by Vogel, K.: The Significance of Arsenic in the Excretions, Am. J. M. Sc. **176**:215-224 (Aug.) 1928.

6. (*a*) Boos, W. F., and Werby, A. B.: Arsenic in Human Tissues and Food Animals: I. So-Called Normal Arsenic, New England J. Med. **213**: 520-527 (Sept. 12) 1935. (*b*) Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1930, p. 485. (*c*) Osterberg, A. E.: Certain Manifestations of Arsenism, Proc. Staff Meet., Mayo Clin. **10**:152-156 (March 6) 1935.

7. Kunkel, A. J.: Handbuch der Toxikologie, Jena, Gustav Fischer, 1899, vol. 1, p. 253.

amount of arsenic, if it exists at all, is so extraordinarily small, hundredths, or even thousandths, of a milligram in an entire organ, that it is not of forensic significance, whereas quantities a hundred or a thousand times larger than that are of significance.

In cases of chronic poisoning from a single large dose of an inorganic arsenical compound, the central nervous system (as well as the long bones and the hair) contains more arsenic than do the so-called primary depots, the gastrointestinal canal and liver.[8] The relative arsenical content of the various organs in a case in which organic arsenic is received continuously or intermittently until death occurs lies somewhere between that associated with acute poisoning and that associated with chronic poisoning following a single large dose.[9]

However, after the continued administration of organic compounds of arsenic (such as arsphenamine and its derivatives), amounts less than 0.1 mg. of arsenic per 100 Gm. of fresh tissue are generally to be found in the brain.[10] Exceptions to this general rule are represented by cases of so-called hemorrhagic encephalitis.[10f]

Trivalent compounds of arsenic, both inorganic and organic, interfere directly with the oxidation of tissue in general [11] and cause widespread

8. (*a*) Leibowitz, J.: Die Resorption und Ausscheidung des Arsens und seine Verteilung im Körper, Schweiz. med. Wchnschr. **64**:947-949 (Oct. 13) 1934. (*b*) McNally, W. D.: The Retention of Arsenic in the Organs, J. Am. Chem. Soc. **39**:826-828 (April) 1917.

9. Underhill, F. P.: The Distribution of Arsenic in a Human Body, J. Biol. Chem. **19**:513-515, 1914. Petrén.[3a]

10. (*a*) Myers, C. N., and Cornwall, L. H.: Normal Arsenic and Its Significance from the Point of View of Legal Medicine, Am. J. Syph. **9**:647-703 (Oct.) 1925. (*b*) Ullmann, K.: Krebsbildung in der Gewerbemedizin und ihre Beziehungen zur experimentellen Geschwulstforschung, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, p. 615. (*c*) Kolls, A. C., and Youmans, J. B.: Quantitative Studies with Arsphenamine in Blood and Tissues, Johns Hopkins Hosp. Rep. **34**:149-151 (May) 1923; (*d*) II. Distribution and Excretion After Intravenous Injection, ibid. **34**: 181-184 (July) 1923. (*e*) Voegtlin, C.; Smith, M. I.; Dyer, H., and Thompson, J. W.: Penetration of Arsenic into the Cerebrospinal Fluid, with Particular Reference to the Treatment of Protozoal Infections of the Central Nervous System, Pub. Health Rep. **38**:1003-1021 (May 11) 1923. (*f*) Osterberg, A. E., and Kernohan, J. W.: The Presence of Arsenic in the Brain and Its Relation to Pericapillary Hemorrhages or So-Called Acute Hemorrhagic Encephalitis, Am. J. Clin. Path. **4**:362-369 (July) 1934. (*g*) Brahme, L.: Arsen in Blut- und Cerebrospinalflüssigkeit, Acta med. Scandinav. (supp.) **5**:1-240, 1923.

11. (*a*) Warburg, cited by Voegtlin, Rosenthal and Johnson. (*b*) Voegtlin, C.; Rosenthal, S. M., and Johnson, J. M.: The Influence of Arsenicals and Crystalline Glutathione on the Oxygen Consumption of Tissues, Pub. Health Rep. **46**:339-354 (Feb. 13) 1931. (*c*) Szent-Györgyi, cited by Oelkers and Vincke. (*d*) Oelkers, H. A., and Vincke, E.: Beitrag zur Wirkungsweise des Arsens und des Antimons, Arch. f. exper. Path. u. Pharmakol. **182**:499-503, 1936. (*e*) Voegtlin, Dyer and Leonard, cited by Voegtlin.[10e] (*f*) Heubner, cited by Lendle and Reinhardt.[12a] (*g*) Brahme.[10g]

paralysis of arterioles, capillaries and venules.[12] This vasomotor paralysis subsequently aggravates the embarrassment of tissue respiration.

The effects on the brain and spinal cord of arsenical compounds of all three groups (inorganic,[13] organic pentavalent[14] and organic trivalent)[15] are identical. These effects are what might be expected

12. Lendle, L., and Reinhardt, E.: Untersuchungen über den Mechanismus der Arsenwirkung, Arch. f. exper. Path. u. Pharmakol. **162**:585-604, 1931. (*b*) Schmiedeberg, cited by Hulst.[15k] (*c*) Heubner, W.: Ueber die Wirkung von intravenösen Infusionen mit Aurum-Kalium cyanatum, München. med. Wchnschr. **1**:357 (Feb. 18) 1913. (*d*) Loeb, A.: The Action of Arsenic on the Blood Vessels, abstracted, Chem. Abstr. **6**:2788 (Oct. 10) 1912. (*e*) Luithlen, F., cited by Hulst.[15k] (*f*) Ellinger, P., and Schmitt, J.: Ueber den Angriffspunkt der Arsenwirkung, Arch. f. exper. Path. u. Pharmakol. **171**:250-259, 1933. (*g*) Ricker, G., and Knape, W.: Mikroskopische Beobachtungen am lebenden Tier über die Wirkung des Salvarsans und des Neosalvarsans auf die Blutströmung, Med. Klin. **2**:1275-1280 (Aug. 4) 1912. (*h*) Ricker, G., and Foelsche, R.: Quecksilber und Salvarsan in ihrer Wirkung auf die Blutströmung nach mikroskopischen Beobachtungen am lebenden Tier, ibid. **2**:1253-1257 (Aug. 3) 1913. (*i*) Siengalewicz, S. S.: The Action of Neo-Salvarsan and Carbon Monoxide on the Choroid Plexus and Meninges, J. Pharmacol. & Exper. Therap. **24**:289-299 (Nov.) 1924. (*j*) Heubner.[11f]

13. (*a*) Popow, N.: Ueber die Veränderungen im Rückenmarke nach Vergiftung mit Arsen, Blei und Quecksilber, Virchows Arch. f. path. Anat. **93**:351-366, 1883. (*b*) Alexander, S., cited by Henschen.[13d] (*c*) Busse, O., and Merian, L.: Ein Todesfall nach Neosalvarsaninfusion, München. med. Wchnschr. **59**: 2330-2333 (Oct. 22) 1912. (*d*) Henschen, S. E.: On Arsenical Paralysis, Nova acta reg. Soc. scient. upsal. **15**:1-19, 1893. (*e*) Erlicki, A., and Rybalkin: Ueber Arseniklähmung, Arch. f. Psychiat. **23**:861-895, 1892. (*f*) Oppenheim, H.: Ueber einen bemerkenswerten Fall von Intoxikationserkrankung des Nervensystems (chronische Arsen-Antimonvergiftung?), Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:345-370, 1910.

14. Shimazono, J.: Ueber das Verhalten der zentralen und der peripheren Nervensubstanz bei verschiedenen Vergiftungen und Ernährungsstörungen, Arch. f. Psychiat. **53**:972-1094 (March) 1914. Köster, G.: Klinischer und experimentellpathologischer Beitrag zur Atoxylvergiftung, Fortschr. d. Med. **27**:1153-1157, 1909. Black, W. C.: Death from Hemorrhagic Encephalitis Following Treatment with Sulpharsphenamine: Report of Two Cases in Syphilitic Infants, Am. J. Dis. Child. **51**:609-613 (March) 1936.

15. (*a*) Silbermann, O.: Ueber intravitale Blutgerinnungen, hervorgerufen durch toxische Gaben gewisser Arzneikörper und anderer Substanzen, Deutsche med. Wchnschr. **14**:504-505 (June 21) 1888. (*b*) von Marschalkó, T., and Vesprémi: Experimentelle und histologische Studien über Salvarsantod, Arch. f. Dermat. u. Syph. **112**:813-815, 1912; (*c*) Histologische und experimentelle Studien über den Salvarsantod, ibid. **114**:589-610, 1912. (*d*) Kolmer, J. A., and Lucke, B.: A Study of the Histologic Changes Produced Experimentally in Rabbits by Arsphenamin, Arch. Dermat. & Syph. **3**:483-514 (April) 1921; (*e*)

(Footnote continued on next page)

on the basis of the pharmacodynamic action of these compounds. The primary interference with tissue oxidation is marked by nonspecific changes in the bodies of the nerve cells. The vasomotor paralysis leads primarily to engorgement of the smaller vessels and to edema of the central nervous system. Subsequent fatty degeneration of the endothelium of these vessels leads to the formation of thrombi and peri-

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A Study of the Histologic Changes Produced Experimentally in Rabbits by Neoarsphenamin, ibid. **3**:515-530 (April) 1921. (*f*) Doinikow, B.: Ueber das Verhalten des Nervensystems gesunder Kaninchen zu hohen Salvarsandosen, München. med. Wchnschr. **1**:796-798 (April 15) 1913. (*g*) Osborne, E. D.; Putnam, S. D., and Hitchcock, B. S.: The Effect of Arsenic on Rabbits: Microchemical Studies Following the Administration of the Arsphenamines and Tryparsamide, Arch. Dermat. & Syph. **25**:419-437 (March) 1932. (*h*) Janeso, cited by Dobszay, László and Dubrausky, V.: Untersuchungen zur Pharmakologie und Pharmakodynamie des Kindesalters: XII. Das Salvarsan, Arch. f. Kinderh. **110**:154-160, 1937. (*i*) Scott, E., and Moore, R. A.: Fatalities Following the Use of Arsphenamine, Am. J. Syph. **12**:252-262 (April) 1928. (*j*) Stühmer, A.: Die Hirnschwellung nach Salvarsan: Wege zu ihrer Vermeidung und therapeutischen Beeinflussung, München. med. Wchnschr. **1**:96-98 (Jan. 24) 1919. (*k*) Hulst, J. P. L.: Einige Bemerkungen über einen Todesfall nach einer intravenösen Neosalvarsan-Injektion, Virchows Arch. f. path. Anat. **220**:346-362 (Oct. 16) 1915. (*l*) Pritzi, O.: Ein Fall von Salvarsanencephalitis in der Schwangerschaft, Zentralbl. f. Gynäk. **52**:2930-2936 (Nov. 17) 1928. (*m*) Fischer, B.: Ueber Todesfälle nach Salvarsan, Deutsche med. Wchnschr. **2**:908-910 (July 29); 939-942 (Aug. 5); 976-978 (Aug. 12) 1915. (*n*) Globus, J. H., and Ginsburg, S. W.: Pericapillary Encephalorrhagia Due to Arsphenamine: So-Called Arsphenamine Encephalitis, Arch. Neurol. & Psychiat. **30**:1226-1247 (Dec.) 1933. (*o*) Gunn, J. A., and Felthan, W. J.: The Antihaemolytic Action of Arsenic, Brit. M. J. **1**:134-135 (Jan. 21) 1911. (*p*) Kirschbaum, M. A.: Ueber kapillare Gehirnblutungen, Frankfurt. Ztschr. f. Path. **23**:444-470, 1920. (*q*) Wechselmann and Bielschowsky, cited by Weimann.[25b] (*r*) Wolff, K.: Beitrag zur Morphologie der Kreislaufstörungen im Gehirn. Bau und Entstehung der Ringblutungen, Virchows Arch. f. path. Anat. **298**:98-160, 1936. (*s*) Alpers, B. J.: So-Called "Brain Purpura" or "Hemorrhagic Encephalitis:" A Clinicopathologic Study, Arch. Neurol. & Psychiat. **20**:497-523 (Sept.) 1928. (*t*) Schmerl, G.: Encephalitis haemorrhagica nach Salvarsaninjektionen, München. med. Wchnschr. **2**: 1685-1686 (July 29) 1913. (*u*) Blitch, C. G.: Post-Arsenical Hemorrhagic Encephalitis and Report of Case, Mil. Surgeon **80**:385-387 (May) 1937. (*v*) Russell, D. S.: Changes in the Central Nervous System Following Arsphenamine Medication, J. Path. & Bact. **45**:357-366 (Sept.) 1937. (*w*) Spielmeyer, cited by Alpers.[15s] (*x*) Pollak, E., and Riehl, G., Jr.: Zur Pathologie der Salvarsanschäden des Nervensystems, Jahrb. f. Psychiat. u. Neurol. **47**:99-127 (Jan. 31) 1930. (*y*) Bayet, cited by McCaskey, G. W.: Salvarsan and Neosalvarsan Myelitis: Report of a Fatal Case, J. A. M. A. **69**:1960-1962 (Dec. 8) 1917. (*z*) Spiethoff, cited by Socin.[15b'] (*a'*) Chiari, H.: Ueber eine nach Neosalvarsaninjektionen aufgetretene "Myelitis," Verhandl. d. deutsch. path. Gesellsch. **16**:155-161, 1913. (*b'*) Socin, C.: Ueber Salvarsan-Myelitis, Cor.-Bl. f. schweiz. Aerzte **46**:1560-1580, 1916.

vascular changes, namely, necrosis, gliosis and hemorrhages. Emboli, perhaps consisting of Voegtlin's protein-arsphenamine precipitate,[16] may play a role.

Finally, if the patient survives three or four days, mesodermal elements (at first polymorphonuclear cells) infiltrate the regions of perivascular necrosis. Later, the walls of the vessels become hyalinized and those mesodermal elements associated with chronic inflammation (lymphocytes and plasma cells) appear in the form of perivascular cuffs, that is, an inflammatory reaction occurs.

For many years neuropathologists attempted to draw a distinction between essential or primary inflammatory disease of the brain, on the one hand, and "inflammatory reactions," on the other. They expressed the belief that the first group of designations should be restricted to "inflammatory diseases of the brain of infectious origin, no matter whether or not the infectious agent is identified."[17] Although Jakob[18] stated that lymphocytic infiltration in cases of encephalomyelitis signifies the presence of bacterial infection and Pette[19] asserted that it indicates a virus infection, Spielmeyer[20] has clearly enunciated the nonspecificity of each of the components of the encephalitic reaction. He stated[21] that if an injury induces a defensive reaction on the part of the living organism the pathologic lesion in general is the same regardless of the nature of the injurious agent: visible or invisible germs, toxic or infectious injury, exogenous poison or even endogenous metabolic or destructive processes. The same mechanism of defense is put into action in any case. Spielmeyer's views, which are now widely accepted, may have evolved from those of Oppenheim and Cassirer,[22] who stated that, by and large, all agents that can damage the organism either through intoxication or through infection can lead to severe alterations in the brain itself, by way of the blood stream. The hematogenous character

16. Voegtlin, C.: The Pharmacology of Arsphenamine (Salvarsan) and Related Arsenicals, Physiol. Rev. **5**:63-94 (Jan.) 1925.

17. Globus, J. H.: Inflammatory Disease of the Central Nervous System: So-Called Nonsuppurative Encephalitis and Encephalomyelitis, Arch. Neurol. & Psychiat. **28**:810-843 (Oct.) 1932.

18. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **27**:290-320, 1915.

19. Pette, H., cited by Globus.[17]

20. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, vol. 1.

21. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161-203, 1930.

22. Oppenheim and Cassirer, cited by Vogt, H.: Encephalitis nonpurulenta, in Lewandowsky, M.: Handbuch der Neurologie: Spezielle Neurologie II, Berlin, Julius Springer, 1912, vol. 3, pp. 229-264.

of the lesion can be seen in the changes which begin in the neighborhood of the blood vessels, especially near the small vessels. Recently, Globus [17] also pointed out the striking confluence of all the forms of encephalitis.

Before we consider the question whether arsenic was the etiologic agent in any of our cases, it may be well to observe the effects of the long-continued action of other chemical substances. It is now known that the encephalitic reactions are nonspecific and that typical inflammatory changes have been caused by the intracarotid injection of various agents.[23] Similar lesions have resulted from the experimental introduction of certain substances, such as trypan blue, into the spinal fluid or cerebral tissue.[24] Inflammatory cells have been reported in cases of chronic poisoning from lead,[25] manganese,[26] cocaine,[27] cyanide,[25a] carbon monoxide [28] and mushrooms.[29]

In judging whether perivascular infiltration may result from exogenous toxins the element of time must be considered. At least a few days are required for the development of such infiltration. Even after long-continued exposure to poison, one cannot expect to find encephalitis unless there had been clinical evidence that the brain was affected. With these two factors, apparently dissonant neuropathologic reports may be harmonized. From the evidence presented, it is clear that "chemical encephalitis," a term suggested by one of us (Kernohan), is not rare.

MATERIAL AND METHODS

General Plan.—Three series of cases in which death was unquestionably attributable to arsenical poisoning were studied from the clinical, pathologic and chemical points of view. Cases 1 to 4 (table 1) represent instances in which a large dose of inorganic arsenic was ingested and in which death occurred

23. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:797-810 (April) 1938.

24. Wertham, F.: The Nonspecificity of the Histologic Lesions of Dementia Paralytica, Arch. Neurol. & Psychiat. **28**:1117-1138 (Nov.) 1932.

25. (*a*) Ferraro, A., cited by Bertrand, I., and Miyashita, K.: Le problème des périvascularites toxiques, Rev. neurol. **65**:409-416, 1936. (*b*) Weimann, W.: Intoxikationen, in Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7, pp. 42-96. (*c*) Dürck, cited by Weimann.[25b]

26. Lewy, F. H., and Tiefenbach, L.: Die experimentelle Manganperoxyd-Encephalitis und ihre sekundäre Autoinfektion, Ztschr. f. d. ges. Neurol. u. Psychiat. **71**:303-320, 1921.

27. Brack, E.: Ueber Hirnarterien-Veränderungen, speziell bei Vergiftungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:526-531, 1928.

28. Altschul, R., cited by Bertrand, I., and Miyashita, K.: Le problème des périvascularites toxiques, Rev. neurol. **65**:409-416, 1936.

29. Marcovitz, E., and Alpers, J., cited by Bertrand, I., and Miyashita, K.: Le problème des périvascularites toxiques, Rev. neurol. **65**:409-416, 1936.

within twenty-four hours. Cases 5, 6 and 7 (table 1) represent instances in which death occurred within a few days and in which significant amounts of arsenic were found in the viscera, even though arsenical poisoning had not been suspected clinically. Cases 8 to 13, inclusive (table 2), represent instances of so-called hemorrhagic encephalitis in which appreciable amounts of arsenic were found in the brain. Cases 1 to 13, inclusive (tables 1 and 2), therefore, represent instances of known arsenical poisoning.

Subsequently, a large miscellaneous group of cases listed in the neuropathologic files of the Mayo Clinic under the heading of "encephalitis" was considered. First, the brain tissues which had been preserved in a solution of formaldehyde were tested for the presence of arsenic. In accordance with Osterberg's suggestion, the finding of 0.1 mg. of arsenic per 100 Gm. of tissue was considered

TABLE 1.—*Cases of Acute Fatal Poisoning with Inorganic Arsenical Compounds*

Case	Sex	Age, Years	Survival After Onset of Symptoms	Mg. of Arsenic per 100 Gm.	
				Brain	Liver
1	M	4	10 hours	0.08	0.56*
2	F	50	? hours	0.12	1.02*
3	M	4	24 hours	0.37	0.138*
4	M	45	24 hours	0.25	1.00*
5	F	1	4 days	Trace	1.7
6	M	7	5 days	0.05	0.10
7	M	41	8 days	0.10	Nil

* Arsenic was found also in the gastric content.

TABLE 2.—*Cases of So-Called Hemorrhagic Encephalitis*

Case	Sex	Age, Years	Survival After Onset of Symptoms	Mg. of Arsenic per 100 Gm.	
				Brain	Liver
8	M	40	1 day	0.18	Nil
9	F	32	4 days	0.12	0.125
10	F	36	5 days	0.20	Nil
11	M	32	Few days	0.10	0.10
12	F	41	6 days	0.20	Nil
13	M	29	8 days	0.12	0.135

significant. Instances in which the brain contained such amounts were designated as positive cases. Other instances in which less than this amount of arsenic was present were called negative, or control, cases (cases 14 to 37). After the presence or absence of arsenic had been determined, the clinical records were studied for evidence of the presence of syphilis. In the event that there was any clinical evidence of syphilis the case was withdrawn from our consideration in order to avoid unnecessary confusion. The prevalence of the use of arsenical compounds in the treatment of syphilis would interfere with proper interpretation of the chemical findings, and the possible presence of syphilitic meningoencephalitis might complicate the interpretation of the neuropathologic findings. Cases 44 to 55, inclusive (tables 3 and 4), constitute the remaining positive cases in our series and represent the main object of this study.

Chemical Methods.—For determining the presence of arsenic in the brain and liver, Osterberg's [30] modification of the electrolytic Gutzeit apparatus was used.

30. Osterberg, A. E.: A Modification of the Electrolytic Gutzeit Apparatus for the Estimation of Arsenic in Biological Material, J. Biol. Chem. **76**:19-22 (Jan.) 1928.

Five grams of tissue was used in all of the determinations on brain and in all but two or three of the determinations on liver, in which only smaller amounts of tissue were available.

It was important to determine whether the arsenic in the brain might have resulted from the use of embalming fluids. Accordingly, samples of the eight embalming fluids used by all the undertakers who embalmed the brains in these cases were tested for their content of arsenic. One specimen did not contain arsenic. In 1 case there was 0.02 mg. of arsenic; in 4 cases, 0.04 mg., and in 2 cases, 0.4 mg., per hundred cubic centimeters of fluid. If the maximal concentration found in these cases had been used, that is, a solution containing 0.4 mg. of arsenic per hundred cubic centimeters of embalming fluid, and if 1,000 cc. of the fluid had been used 4 mg. of arsenic would have been injected. It is hardly conceivable that all this arsenic would have remained in the body, for several washings of extremely dilute fluid are used. The average dilution of embalming fluid is 12 parts of water to 1 part of fluid. But even if all the arsenic were deposited in the body, it is altogether unreasonable to suppose that 37 per cent of the arsenic would remain in the brain, an amount which represents the smallest positive figure, namely, 0.1 mg. per 100 Gm. of brain tissue. In many of the significant cases (cases 1, 3, 5, 46, 48 and 49) embalming was not done.

If the brains had not been embalmed before removal, solution of formaldehyde U. S. P. was injected into the circle of Willis in the laboratory. In any event, the brains were stored in a dilute solution of formaldehyde U. S. P. (1:25). Accordingly, chemical analysis of the solution of formaldehyde used in the laboratory was made and arsenic was not found. The fact that arsenic when found in the tissues could not have been the result of contamination by either the embalming fluids or the solution of formaldehyde used in preserving the tissues is amply demonstrated by the large series of control cases (cases 14 to 43, inclusive), in most of which embalming had been performed before necropsy.

Although it is a matter of lesser importance, it was interesting to determine whether arsenic was leached out of the tissues by the formaldehyde in which the organ was preserved. That this did occur is shown by a few cases in which the original arsenical content of unembalmed tissue was found to be several times that of the same tissue after prolonged fixation in formaldehyde. In these cases arsenic could be recovered from the formaldehyde provided that the brain was kept continuously in the same individual container.

However, in many instances an equilibrium was set up between the amount of arsenic in the brain and that in the fluid in which it was preserved. In these cases repeated determinations of arsenic over a period of five years yielded almost identical results (provided that the same region of the brain was used). The difference in results was usually less than 0.06 mg. per 100 Gm. of tissue, and the lower content of arsenic resulted from the more recent determinations.

However, if a brain which has been kept in an individual jar for some time and which has been proved repeatedly to contain an appreciable amount of arsenic is then placed with many other brains in a large crock filled with solution of formaldehyde, most of the arsenic may be leached out of the brain tissue. This observation was made repeatedly.

Accordingly, all of the determinations made on brain tissues and recorded in this study have been carried out either on fresh tissue which had not been stored in solution of formaldehyde at all or on tissue from brains which were stored in small individual containers.

That arsenic is not always distributed homogeneously throughout the substance of the brain was pointed out first by Osterberg and one of us (Kernohan),[10f] who found a greater concentration of arsenic in the white matter than in the gray matter of the brain in their 4 cases of pericapillary hemorrhage. Although in some cases of the present series smaller amounts of arsenic were found in less severely damaged regions of the brain, if arsenic was present at all it was always found in maximal concentration at the site of greatest pathologic change. Whenever more than 0.1 mg. of arsenic per 100 Gm. of brain tissue was found in the cases of subacute or chronic poisoning there was profound histopathologic alteration.

The reliability of the method, apparatus and reagents used is beyond question. They have been used in thousands of determinations in the routine work of the clinic. Indeed, our own controls (cases 14 to 43, inclusive) are evidence in themselves of the reliability of the test. The possibility of an infinitesimal amount of arsenic being present as a contaminant is admitted, but this does not come into consideration so far as the amounts that have been recorded are concerned. Indeed, anything less than 0.02 mg. per 100 Gm. of tissue (corresponding to 0.001 mg. of arsenic actually determined) was considered a negative observation. Our determinations are recorded in terms of elemental arsenic per weight of fresh or wet tissue.

Neuropathologic Methods.—In each case many blocks of tissues were studied. In most instances the tissue was embedded in paraffin and hematoxylin and eosin stains were made first. The other stains used were cresyl violet, Mallory's phosphotungstic acid hematoxylin, Weigert's stain for myelin sheaths, Cajal's gold chloride and mercury bichloride method and the Hortega silver carbonate methods of impregnation. These technics have been described elsewhere.[31]

RESULTS

Cases of Acute Fatal Poisoning from Inorganic Arsenic (Cases 1 to 7).—Whenever the history was available, the symptoms were observed to be typical of those of acute arsenical poisoning: vomiting, headache, diarrhea and, in 2 instances, convulsions. In cases 1 to 4, in which considerable amounts of arsenic were found in the stomach, death occurred within twenty-four hours. In these 4 cases of peracute poisoning the most definite evidence of pathologic change in the brain was in the oligodendroglia, which had become greatly swollen. Also, proliferation of the microglia and cerebral edema were present. There were incipient nonspecific changes, chromatolysis or pyknosis, in the nerve cells. These changes were similar to those of "serous encephalitis" of Brown and Symmers[32] and those of "acute toxic encephalitis" of Grinker and Stone.[33] The pathologic alterations, therefore, must be

31. Kernohan, J. W.: Preparation of Neurologic Material for Histologic Study, Am. J. Clin. Path. **4**:410-425 (Sept.) 1934.

32. Brown, C. L., and Symmers, D.: Acute Serous Encephalitis: A Newly Recognized Disease of Children, Am. J. Dis. Child. **29**:174-181 (Feb.) 1925.

33. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood: A Clinicopathologic Study of Thirteen Cases, Arch. Neurol. & Psychiat. **20**:244-272 (Aug.) 1928.

considered the nonspecific effect of a noxious agent which causes death very rapidly. A fully developed inflammatory reaction was not present.

In cases 5, 6 and 7 the period of survival was from four to eight days. In addition to the observations made in the first group of cases, there were a few perivascular hemorrhages in cases 5 and 6 and some perivascular cells similar to lymphocytes in case 7. As shown in figure 1, these cells were mostly oligodendrocytes. Cases 5, 6 and 7 therefore represent the transitional stage from the peracute forms (cases 1 to 4) to the acute forms of hemorrhagic encephalopathy (cases 8 to 13, table 2) and the subacute and chronic forms (cases 44 to 55, tables 3 and 4). As would be expected, the liver contained much more arsenic than the

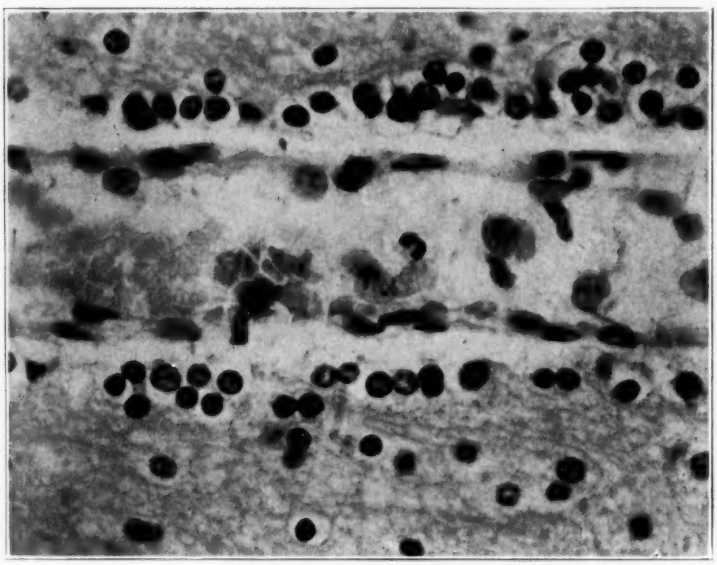

Fig. 1.—Acute swelling and pericapillary aggregation of oligodendroglia cells in the superior frontal gyrus (case 7). Both the endothelial lining and the contents of the capillary are illustrated. Hematoxylin and eosin; × 475.

brain in most cases. The findings in case 3 are exceptional because of the relatively low concentration of arsenic in the liver. The actual amount of arsenic in the brain is consistent with that in the other cases (table 1).

Cases of So-Called Hemorrhagic Encephalitis.—The symptoms of so-called hemorrhagic encephalitis were typical, and included headache, convulsions, coma and focal signs. The pathologic changes were characteristic and included advanced cerebral edema, marked proliferation and acute swelling of the oligodendroglia and widespread hemorrhages. In all cases there were regions of necrosis and demyelination,

which Russell [15v] has emphasized. In 4 of the 6 cases there was the beginning of perivascular infiltration. In 3 cases (9, 11 and 13) there were equal concentrations of arsenic in the brain and the liver, but in 2

TABLE 3.—*Cases of Subacute Encephalitis with Arsenic Present in Brain: Clinical and Chemical Features*

Case	Sex	Age, Years	Clinical Diagnosis	Survival After Onset of Cerebral Symptoms	Mg. of Arsenic per 100 Gm.	
					Brain	Liver
44	M	36	Diffuse encephalomyelitis	5 weeks	0.30	Nil
45	M	½	Malnutrition; cerebral edema ?	16 days	0.30	0.01
46	F	53	Indeterminate psychosis	3½ weeks	0.50	Nil
47	M	36	Encephalitis	5½ weeks	0.22	Nil
48	M	57	Encephalitis	2 months	0.37	Nil
49	M	63	Arsenical poisoning	2 months	0.35	0.06
50	M	65	Probably tumor of aqueduct or fourth ventricle	3 months	0.40	0.01
51	M	37	Tumor of fourth ventricle	4½ months	0.17	Nil
52	M	30	Acute encephalomyelitis	6½ months	0.40	Nil
53	F	19	Subacute lethargic encephalitis	9 months	0.20	Nil
54	F	14	Grand mal epilepsy; athetosis; mental deficiency	Few years	0.83	0.05
55	M	53	Indeterminate psychosis	Few years	0.10	0.04

TABLE 4.—*Microscopic Observations in Cases of Subacute Encephalitis with Arsenic Present in the Brain* *

Case number	44	45	46	47	48	49	50	51	52	53	54	55
Cells in spinal fluid												
Small lymphocytes	41	1	1	53	57	1	5	41	248	2	3	90
Large lymphocytes	3	..	..	..	..	..	..	1	6	..	..	..
Polymorphonuclear leukocytes	2	9	..	..	..	..	..	..	..	..	..	1
Changes in nerve cells												
Chromatolysis	2	2	2	3	2	2	1	2	2	2	2	3
Pyknosis	0	3	0	0	0	0	0	0	0	0	1	0
Satellitosis	1	1	2	2	2	2	2	3	3	2	2	1
Interstitial cells												
Microglia	1	2	2	1	1	1	2	1	1	1	1	1
Oligodendroglia	3	3	3	3	3	3	4	2	4	4	3	3
Perivascular cells												
Endothelial	1	1	0	1	1	1	2	1	1	0	0	1
Lymphocytes	2	0	1	2	1	0	1	2	2	3	2	3
Plasma cells	2	0	1	2	3	1	0	3	2	1	2	2
Oligodendroglia	0	1	1	0	0	1	2	0	1	1	0	0
Edema												
Interstitial	2	3	3	3	2	3	2	2	2	3	2	2
Perivascular	0	1	1	2	0	1	0	1	2	2	0	0
Pericellular	0	1	0	1	0	1	0	1	2	1	0	0
Meninges												
Thickening	1	2	1	1	1	0	2	1	2	0	0	2
Lymphocytes	3	1	0	1	2	2	0	1	2	3	2	2
Plasma cells	3	0	0	1	2	0	1	1	1	1	2	1
Scavenger cells	1	2	0	1	1	0	1	2	2	0	0	1

* Numbers of cells in the spinal fluid are given per cubic millimeter. The significance of the other figures follows: 0 indicates normal, or absence of abnormality; 1, 2, 3 and 4 indicate degrees of pathologic alteration or of increase in number of cells.

cases (8 and 12) there was much more arsenic in the brain than in the liver (table 2).

Main Group of Controls.—This series of cases (cases 14 to 37) included instances of many different types of encephalopathy, of which

only the syphilitic varieties were excluded. The patients ranged in age from less than 1 to 60 years. There was an intracranial lesion in every case, and in many instances some other somatic disorder. Of the 24 brains, 15 contained no arsenic and 9 had 0.02 to 0.05 mg. per 100 Gm. of tissue.

In cases 31 and 32 lesions morphologically identical with those of our main series (cases 44 to 55) were observed. However, repeated examination of the brain revealed the absence of arsenic and apparently demonstrated that these morphologic changes are not specific; however, the arsenic may have been present formerly and may have been excreted before the patient died.

Special Group of Controls.—Since it might be thought that the arsenical compounds circulating through the body may tend to be deposited in a locus minoris resistentiae, we sought a special group of control cases in which the etiologic agent was known and which resembled the cases of encephalitis in duration, symptoms and pathologic changes. Therefore, from 16 instances of fatal, malignant hypertension in which the brain was available for study,[34] we selected those 6 cases in which perivascular "cuffing" (the landmark of encephalitis) with lymphocytes and plasma cells was most severe. Small hemorrhages and multiple infarcts were present in each case. The cellular infiltration was generally from one to three cells deep, and was seen usually in regions of necrosis. Adjacent to the recent infarcts, polymorphonuclear cells were included in these zones of infiltration.

The ages of the patients ranged from 22 to 56. Symptoms had been present from four to eight months before death. Less than 0.02 mg. of arsenic per 100 Gm. of brain tissue was found in each instance.

It is clear that these cases represent instances of diffuse cerebral damage in which cerebral symptoms lasted over a period of months. The fact that arsenic was not found in the brain in a single instance is strong evidence against the hypothesis that arsenic is deposited in the brain in all cases of chronic cerebral damage. This view is substantiated by those other instances of long-standing cerebral disease which are included in the main group of controls (cases 14 to 37).

Subacute Encephalitis Associated with Presence of Arsenic in the Brain (Cases 44 to 55).—A representative instance (case 48) is reported.

A rancher, aged 57, registered at the clinic on Oct. 29, 1937. He complained of generalized weakness, of one month's duration. His past history included tinnitus, vomiting, vertigo and progressive deafness in the right ear. For four or five years the episodes of vertigo and vomiting had been progressive in severity

34. Rosenberg, E. F.: The Brain in Malignant Hypertension, Proc. Staff Meet., Mayo Clin. **14**:217-222 (April 5) 1939.

and frequency. However, his general health had been good until one month before registration. At that time he was chilled for several hours. He had generalized soreness of the muscles for seven to ten days and generalized weakness, which gradually progressed to the point of making him bedridden. There was an occasional mild bifrontal headache. The spinal fluid, examined one week before registration, exhibited normal pressure and a positive Pandy reaction. The concentration of sugar was 15 mg. per hundred cubic centimeters of spinal fluid, and there were 40 cells per cubic millimeter. Of these, 75 per cent were reported as lymphocytes. A pellicle did not form in the spinal fluid, and the results on culturing the fluid and examining the smear were negative. The result of the colloidal gold test was 5555431000.

The patient was apathetic and responded to questions with great effort. The pulse rate, temperature and blood pressure were normal. Examination of the limbs and viscera gave normal results. The cranial nerves were normal except for nystagmus in both the horizontal and the vertical direction and bilateral nerve deafness, more severe on the right side than on the left. Speech was moderately slurred. There was generalized muscular weakness of moderate degree. The abdominal and tendon reflexes were all moderately increased. The Babinski reflex and its confirmatory signs were present on both sides. There were moderate incoordination of all four extremities and some difficulty in successive movements. The patient was unable to stand or walk. The Kernig and Lasègue signs were slightly positive.

Examination of the eyes revealed that the rotations of each eye were somewhat limited in all directions, perhaps because of poor cooperation. Examination of the ocular fundi gave normal results, and the diastolic pressure in the retinal arterioles was normal.

The urine was normal. The concentration of hemoglobin was 15.7 Gm. per hundred cubic centimeters of blood. Erythrocytes numbered 4,440,000 per cubic millimeter of blood and the leukocytes 9,000 to 12,500. The polymorphonuclear neutrophilic leukocytes ranged between 83 and 96 per cent, and the blood smear was not abnormal. The Kline, Kahn, Hinton and Kolmer tests of the blood serum all gave negative results. Agglutination tests of the blood gave negative results for Brucella abortus and for typhoid and paratyphoid bacilli. The concentration of urea in the blood was 48 mg., that of sugar 97 mg. and that of chlorides 566 mg., per hundred cubic centimeters. The sedimentation rate was 10 mm. per hour on one occasion and 3 mm. per hour at a later determination. Roentgenograms of the thorax and head were normal. Examination of the spinal fluid on Oct. 30, 1937 revealed a clear, colorless fluid, under normal pressure. The Kolmer and Kline tests gave negative results, and the total protein measured 15 mg. per hundred cubic centimeters of spinal fluid. There were 57 small lymphocytes, 2 polymorphonuclear cells and a few erythrocytes per cubic millimeter of spinal fluid. The colloidal gold curve was 5552210000. Cultures of the spinal fluid on brain broth and on blood agar did not yield growth of organisms. A Gram stain of the spinal fluid revealed no organisms. The concentration of sugar was 54 mg., and that of chlorides 716 mg. per hundred cubic centimeters of spinal fluid.

The course of the patient's illness was marked by disturbances of consciousness, apathy, restlessness and occasional disorientation. Involuntary incontinence of urine and feces occurred. The pulse rate, temperature and blood pressure remained normal for three weeks. Examination of the spinal fluid was repeated on Nov. 8, 1937. The fluid was clear and colorless and was under a pressure of 19 cm. of

water. Response to compression of the jugular veins was normal. The results of the Kolmer and Kline tests were negative. The total protein was 75 mg. per hundred cubic centimeters of spinal fluid. There were 39 small lymphocytes per cubic millimeter, but neither polymorphonuclear cells nor erythrocytes were present. The colloidal gold reaction was 5555321000. The concentration of sugar in the spinal fluid was 55 mg. per hundred cubic centimeters. Cutaneous tests revealed a strongly positive reaction to stock encephalitis serum and to Los Angeles poliomyelitis serum. Accordingly, the corresponding intramuscular injections of serum were given. Repeated examinations of the ocular fundi gave normal results. Occasionally, intravenous injections of a physiologic solution of sodium chloride and of dextrose were necessary to maintain a proper intake of fluid. Although nasal feeding was instituted, the patient became weaker rapidly. On November 20 the temperature, pulse rate and respiratory rate increased. Evidence of bronchopneumonia appeared. Death occurred on November 22.

Necropsy was performed two hours after death, and before embalming was done. A bacteriologic culture of the heart's blood resulted in absence of growth. A specimen of the blood was sent to Dr. Thomas Rivers, of the Rockefeller Institute, in New York. He reported the absence of neutralizing antibodies for virus of lymphocytic choriomeningitis. Chemical examination of 100 Gm. of brain for the presence of lead gave negative results. However, 0.37 mg. of arsenic per hundred grams of brain tissue was found. Examination of the viscera revealed bronchopneumonia, a chronic gastric ulcer and chronic tuberculosis of the lymph nodes of the hilus of the lung, the liver and the spleen.

Macroscopic examination of the central nervous system gave normal results. Microscopic study revealed severe encephalitis, marked by a profound degree of perivascular infiltration with lymphocytes and plasma cells (fig. 2). Also, chronic meningitis was present (table 4).

Summary of Clinical Observations: There were 9 male and 3 female patients in this group (table 3). The ages ranged from 4 months to 65 years. The duration of life from the onset of cerebral symptoms varied from sixteen days to a few years. Although some indication of diffuse cerebral disturbance was recognized in each case, the evidence was not suggestive of specific cerebral localization. Usually neurologic examination revealed drowsiness, generalized weakness, nystagmus when the patient attempted to look to either side and the Babinski response, which could be elicited on both sides. The clinical diagnosis of arsenical poisoning was made in only 1 case (case 49), and this by Dr. H. W. Woltman. The clinical course in these cases may be described as that of progressive diffuse cerebral failure. There was usually a history of fatigue and perhaps of mild headache for some weeks or months. Then the patient became bedridden and progressively weaker, passed into coma and died.

Although one could arbitrarily designate those forms in which the patient survived a few weeks as "subacute" and the others as "chronic," there is no correspondingly sharp demarcation in the alterations of the tissues as seen microscopically. This apparent discrepancy between

clinical and pathologic observations is probably explained by the fact that diffuse minute cerebral lesions may be present for a long time before the patient is aware of any specific symptoms.

Summary of Chemical Observations: The brains contained from 0.10 to 0.83 mg. of arsenic per hundred grams of tissue (table 3). These concentrations are of the same degree as those found in the more acute forms of fatal arsenical poisoning (table 1) and also as those found in cases of so-called hemorrhagic encephalitis due to arsphenamine (table 2). A significant amount of arsenic was not found in the liver in any of these 12 cases. Unfortunately, in most instances the liver was not examined for arsenic until after the specimens had been preserved for

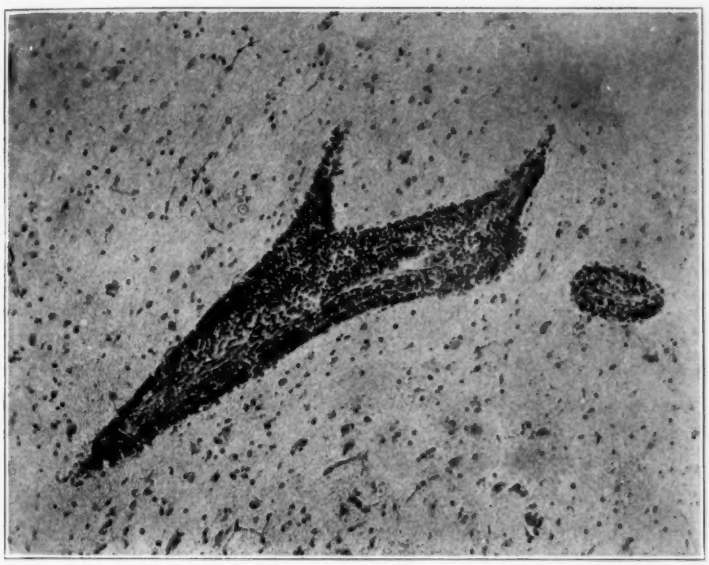

Fig. 2.—Perivascular cells in the thalamus (case 51). Hematoxylin and eosin; × 100.

some time in large crocks of formaldehyde. However, in case 49 the fresh, unembalmed liver was tested, and it was in this case that the hair contained 2.0 mg. and the kidney 0.23 mg. of arsenic per 100 Gm. of tissue, and that 1,443 cc. of urine contained 0.04 mg. of lead and 2.3 mg of arsenic.

Summary of Pathologic Observations: As indicated in table 4, there was frequently an abnormally large number of cells in the spinal subarachnoid fluid. These cells usually were recorded as small lymphocytes, but the likelihood that some of them were plasma cells or oligodendrocytes cannot be denied. The number of cells in the fluid was

generally proportional to the number of cells seen in the meninges on histologic examination. There were erythrocytes and occasional polymorphonuclear cells in the meninges only in the postoperative cases (47, 50 and 51).

Gross examination of the brain in these 12 cases revealed few noteworthy changes. In 5 cases there was slight atrophy of the cortex and in 5 a granular ependyma; in 4 cases the brain was grossly normal, and in 1 case each, edema, congestion and increased density of the white matter were present.

Chromatolysis of the bodies of the nerve cells was generally present in moderate degree, but it is questionable whether these alterations signify antemortem or postmortem degenerative changes. Pyknosis was generally absent. Moderate degrees of satellitosis and neuronophagia were the rule. Proliferation and swelling of the astrocytes were observed in moderate degree in case 45, that of the infant. Similar "progressive" changes in the astrocytes, but to a lesser degree, were also present in cases 47, 48, 51 and 53. Generally there were marked diffuse proliferation and swelling of the oligodendroglia and slight similar changes of the microglia. These changes are not specific and occur in most of the brains obtained in cases in which coma or other evidence of diffuse cerebral impairment has occurred before death. There were focal collections of microglia and oligodendroglia cells only in case 45. Since the brain in this case was that of an infant, these circumscribed aggregations of cells must be considered as normal features, possible germinal centers, and not as evidence of inflammation.[35] In no case was there severe change in the walls of the vessels or in their lumens. Neither thrombosis nor embolism was observed. Slight proliferation of the intima was present in some cases.

Perivascular aggregations of mesodermal elements were present in all cases, and were usually observable under low magnification. The perivascular cells were numerous (figs. 2 and 3) in all cases except 44, 46, and 49. Except in these 3 cases, evidence of a widespread inflammatory reaction could be found in every part of the central nervous system, from the frontal poles to the conus medullaris. The gray and the white matter were equally affected. In the 3 exceptional cases there was a lesser degree of infiltration around the small blood vessels in various parts of the nervous system. Even in these cases there was no apparent site of election for the perivascular cells. Since polymorphonuclear cells were rarely noted among the infiltrates, they are not listed in table 4. Usually the perivascular cellular infiltrates were more profuse in the

35. Schwarz, H.; Goolker, P., and Globus, J. H.: The Normal Histology of Infants' Brains, with Particular Reference to Anatomic Changes in the Brain in Intestinal Intoxication of Infants, Am. J. Dis. Child. **43**:889-913 (April) 1932.

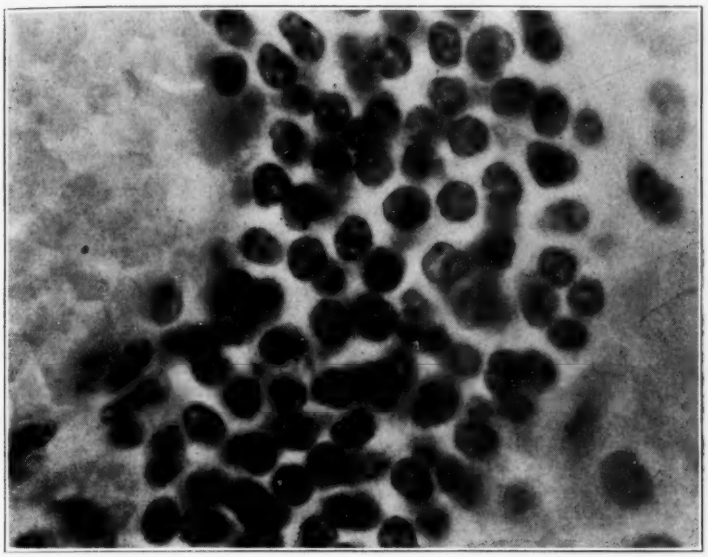

Fig. 3.—Perivascular aggregation consisting largely of plasma cells in the left temporal lobe (case 48). Hematoxylin and eosin; × 1,150.

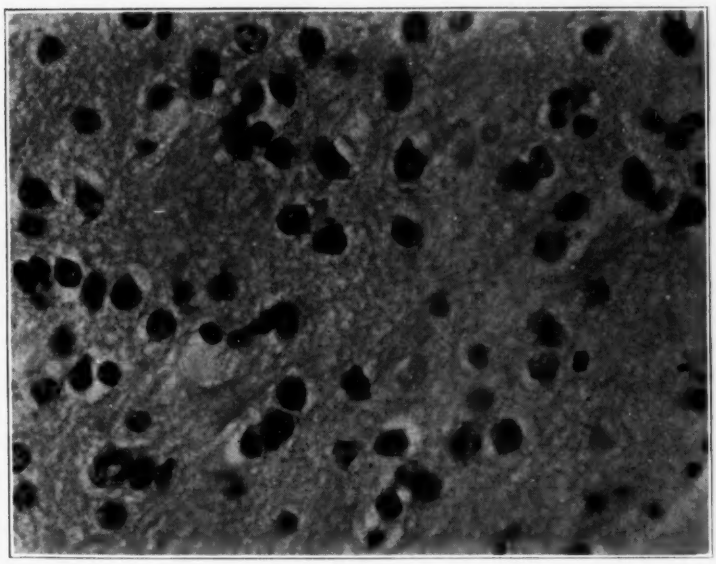

Fig. 4.—Diffuse proliferation and swelling of oligodendroglia cells near the calcarine fissure (case 50). Hematoxylin and eosin; × 475.

cases in which the condition was of longer duration. However, neither the number nor the kind of cells was related to the amount of arsenic in the tissue.

In all cases there was interstitial cerebral edema of moderate degree (figs. 1 and 4). The clear spaces around the ganglion cells and the blood vessels, which are recorded in table 4 as indicating pericellular and perivascular edema, respectively, do not represent certain evidence of antemortem change. Stains for iron, which were made in each case, failed to reveal the presence of this substance in the microglia, the adventitial coats of the vessels or anywhere else in the tissues. There were no regions of demyelination, perivascular, subependymal or otherwise. In brief, the histopathologic changes were those of subacute or chronic disseminated meningoencephalomyelitis. It is now being accepted [36] that this disease includes a heterogeneous group of conditions.

Etiologic Considerations: Evidence of syphilis was not obtained from the history in any of these cases (44 to 55). Serologic tests for syphilis were performed on the blood in each case and on the cerebrospinal fluid in all but 1 case (45). All these serologic tests yielded negative results. Evidence of syphilis was not found in any of the tissues of the body, although a complete necropsy was performed in each case.

In all the cases the fatal termination occurred between 1924 and 1937. In no instance did the symptoms begin at the time of the pandemics of influenza and lethargic encephalitis (1917 to 1920). Furthermore, there was neither clinical nor pathologic evidence of the chronic forms of lethargic encephalitis. The slowly progressive course in these cases excludes the type of encephalitis seen in St. Louis in 1933 and in Australia in 1917 and 1918 and that type of equine encephalomyelitis recently reported to occur in human beings.

All of the investigations for other well recognized etiologic factors have proved fruitless. Many bacteriologic studies of the blood, cerebrospinal fluid and tissues in these cases have failed to yield a pathogenic organism.

We now come to the question whether arsenic should be considered the main pathogenic agent in cases 44 to 55. First, there is no doubt that the amounts of arsenic found in the brains in these cases are abnormally large. This observation, in itself, does not imply that arsenic is the cause of the condition, for it is possible that the arsenic which most Americans ingest and which must circulate in the blood stream before being excreted might be deposited at a locus minoris resistentiae in greatest concentration. To consider this possibility, a special control

36. Grinker R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

group of cases was studied. These cases (38 to 43) resembled the cases of encephalitis in duration, symptoms and pathologic alterations, but the condition was attributable to a well recognized cause, namely, malignant hypertension. The fact that an appreciable amount of arsenic was not found in the brain in a single instance is strong evidence against the likelihood that arsenic is deposited in all brains which have been diffusely damaged over a period of months. Similar evidence is adduced from a consideration of those other instances of cerebral disease of long standing in which arsenic was not found in the brain and which are included in the main control group of cases (14 to 37).

RECAPITULATION

Well recognized chronic arsenical poisoning frequently is manifested by diffuse cerebral symptoms: fatigue, headache, vertigo, drowsiness and impairment of mental activity. These are precisely the same symptoms from which the patients in this group (cases 44 to 55) suffered and which constitute a syndrome that is summarized as "progressive diffuse cerebral failure."

The toxic effect of arsenic on the nervous system is not specific and is marked by alterations in the ganglion cells and by regions of perivascular necrosis. In subacute and chronic forms these regions of necrosis become filled with lymphocytes and plasma cells. In the cases in this series such changes were exhibited.

The actual concentrations of arsenic in the brain (0.1 mg. of arsenic or more per hundred grams of brain tissue) in these cases were abnormally large. These concentrations were the same as those found in cases of acute arsenical poisoning due to either inorganic or organic compounds of arsenic, and recorded both in the literature and in our own series of such cases.

Therefore all the observations, clinical, pathologic and chemical, that concern these 12 cases of subacute encephalomyelitis are consistent with the hypothesis that they represent instances of chronic arsenical poisoning. Further evidence for or against this hypothesis can be obtained by microscopic studies of brains in cases of recognized chronic arsenical poisoning and by the determination of the content of arsenic in the excreta and tissues, especially the nervous system and hair, in other cases of subacute or chronic meningoencephalomyelitis.

DISTRIBUTION OF NERVE TERMINALS (*BOUTONS*) IN THE HUMAN SPINAL CORD

QUANTITATIVE STUDIES

JEFF MINCKLER, PH.D.
OMAHA

Reports of changes in the nerve terminals (end bulbs, *Endfüsse, boutons*) about the nerve cells of the spinal cord of animals following experimental resection of nerve tracts and peripheral nerves (Marinesco [1]; Marui [2]; Miskolczy [3]; Hoff [4]; Foerster, Gagel and Sheehan [5]; Hoff and Hoff [6]; Fulton, Hoff and Kennard [7]; Snider [8]; Gibson [9]; Barnard,[10] and Schimert [11]) naturally raise the question of the normal morphologic characteristics of these structures and their reac-

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This study was carried on in the Department of Anatomy, University of Minnesota, under the direction of Dr. A. T. Rasmussen. Dr. Edith Boyd supervised the quantitative work.

1. Marinesco, G.: Recherches sur la structure de la partie fibrillaire des cellules nerveuses à l'état normal et pathologique, Rev. neurol. **12**:405-428, 1904.

2. Marui, K.: The Effect of Over-Activity on the Morphological Structure of the Synapse, J. Comp. Neurol. **30**:253-282, 1918.

3. Miskolczy, D.: Die Endigungsweise der olivo-cerebellären Faserung, Arch. f. Psychiat. **102**:197-201, 1934.

4. Hoff, E. C.: Central Nerve Terminals in the Mammalian Spinal Cord and Their Examination by Experimental Degeneration, Proc. Roy. Soc., London, s.B **111**:175-188, 1932.

5. Foerster, O.; Gagel, O., and Sheehan, D.: Veränderungen an den Endösen im Rückenmark des Affen nach Hinterwurtzeldurchschneidung, Ztschr. f. Anat. u. Entwcklngsgesch. **101**:553-565, 1933.

6. Hoff, E. C., and Hoff, H. E.: Spinal Terminations of the Projection Fibres from the Motor Cortex of Primates, Brain **57**:454-474, 1934.

7. Fulton, J. F.; Hoff, E. C., and Kennard, M. A.: Corticospinal Pathways from the Premotor Area, Tr. Am. Neurol. A. **60**:32-36, 1934.

8. Snider, R. S.: Alterations Which Occur in Mossy Terminals of the Cerebellum Following Transection of the Brachium Points, J. Comp. Neurol. **64**:417-435, 1936.

9. Gibson, W. C.: Degeneration of the *Boutons Terminaux* in the Spinal Cord, Arch. Neurol. & Psychiat. **38**:1145-1157 (Dec.) 1937.

10. Barnard, R. I.: Experimental Changes in End Feet, Anat. Rec. (supp. 3) **70**:6-7, 1938.

11. Schimert, J.: Die Endigungsweise des Tractus vestibulospinalis, Ztschr. f. Anat. u. Entwcklngsgesch. **108**:761-767, 1938.

tions to pathologic conditions in the human spinal cord. It has been found (Minckler [12]) that the *boutons* of human spinal cords obtained at routine autopsies stain surprisingly well by the Cajal block silver method as used by Barr.[13] Examination of 68 specimens revealed that the terminals could be classified into five primary morphologic groups ("types")—small loops, large loops, filamented loops, fibrillated bulbs and opaque or granular masses—and each of these groups into three subgroups ("forms")—regular, thickened and granular—as shown in figure 1. According to serial counts through single nerve cells in optimal preparations, the total number of *boutons* per cell varied from

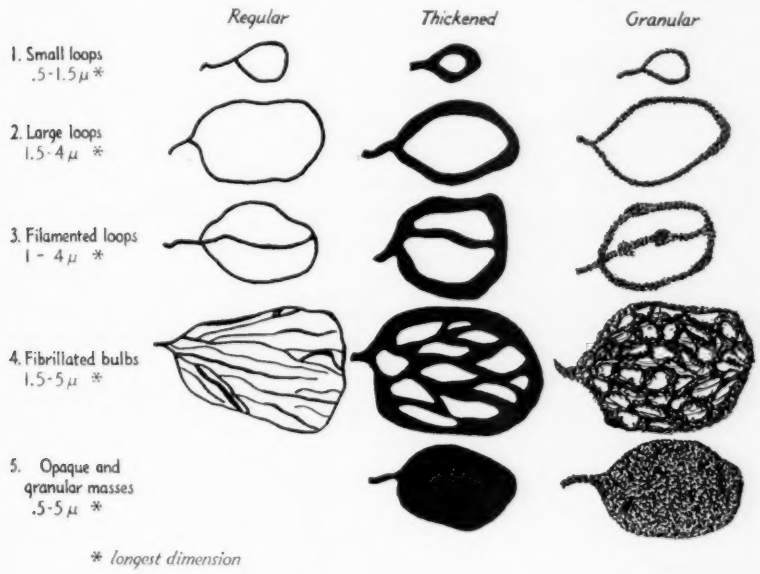

Fig. 1.—Diagrammatic chart of the types and forms of *boutons* as seen in block silver sections. The figures are drawn to scale to illustrate comparative sizes. The measurements given illustrate variations in longest dimensions.

88, on a dorsal sensory cell, to 833, on a posterolateral cell. Because of the difficulty in following cell processes through serial sections, these values represent only totals for cell bodies. Computed values for terminals on an entire ventral horn cell run to several thousand.

Before such data can be of practical value in neuropathology, the effects of age, autolysis and variations in technic incident to routine

12. Minckler, J.: The Morphology of the Nerve Terminals of the Human Spinal Cord as Seen in Block Silver Preparations, with Estimates of the Total Number Per Cell, Anat. Rec. **77**:9-25, 1940.

13. Barr, M. L.: Some Observations on the Morphology of the Synapse in the Cat's Spinal Cord, J. Anat. **74**:1-11, 1939.

autopsy methods must be known. By selection of cases in which there was no indication of significant involvement of the central nervous system an attempt has here been made to evaluate these factors. Since one cannot be assured that all the terminals have been brought into view, the aim has been to establish a normal *bouton* distribution pattern in relative terms, a variation from which would reflect pathologic influence.

TABLE 1.—*Essential Data on the Twenty-Six Cases Used in a Study of the Distribution of Nerve Terminals in the Spinal Cord*

Case No.	Age, Yr.	Autopsy Time	Diagnosis
4	10 mo.	15′ 15″	Acute exudative myocarditis
6	1½	2′ 45″	Wilms's tumor
9	11	14′ 40″	Rheumatic pancarditis
12	16	4′	Seminoma of left testicle
15	23	14′ 20″	Chronic glomerulonephritis; bronchopneumonia
18	36	13′	Amyloid kidneys; uremia
25	46	4′ 20″	Postericoid abscess; probable polycythemia vera
26	47	12′ 20″	Pulmonary and intestinal tuberculosis; fatty cirrhosis of liver
27	50	16′ 30″	Leukemic reticuloendotheliosis; (reticulomyelosis)
32	54	3′ 25″	Streptococcic septicemia
33	54	13′	Essential hypertension; coronary thrombosis
34	55	21′ 30″	Probable Banti's disease
37	57	15′ 10″	Adenocarcinoma of stomach
39	57	11′	Carcinoma of esophagus
41	58	8′	Essential hypertension; bronchopneumonia
42	59	16′ 50″	Crushing injuries of chest
44	61	2′ 40″	Arteriosclerotic hypertensive heart disease
45	62	4′	Carcinoma of stomach; diabetes mellitus; pulmonary embolism
49	69	7′	Substernal thyroid
50	69	4′ 45″	Cicatricial occlusion of common bile duct
51	70	2′ 30″	Coronary sclerosis
52	71	2′ 45″	Chronic pancreatitis
53	72	6′ 45″	Diabetes mellitus; coronary sclerosis; myocardial infarct
54	73	5′	Acute perforation of a duodenal ulcer with generalized peritonitis
56	76	7′ 15″	Carcinoma of common hepatic duct with metastases
59	83	8′ 30″	Carcinoma of cystic duct

TABLE 2.—*Absolute and Relative Number of Nerve Terminals on One Side of a 10 Micron Section Through the Fourth Lumbar Segment in Case 53*

Type	Regular		Thickened		Granular		Total	
	No.	Per-centage	No.	Per-centage	No.	Per-centage	No.	Per-centage
Small loops	1,120	34.5	28	0.83	373	11.04	1,561	46.24
Large loops	905	26.8	29	0.85	321	9.52	1,255	37.17
Filamented loops	13	0.3	2	0.06	6	0.17	21	0.62
Fibrillated bulbs	265	7.8	3	0.09	249	7.37	517	15.32
Opaque and granular masses	.....	....	4	0.12	18	0.54	22	0.65
Total	2,343	69.4	66	1.95	967	28.64	3,376	100

MATERIAL AND METHOD

The data reported here are based on the study of 26 selected spinal cords in cases in which there was no clinical evidence of damage to the cord. In table 1 these cases are listed according to age; the autopsy time (time elapsing between death and fixation) and the diagnosis are included.

The gross and microscopic technics used in obtaining and preparing the material, as well as the method of counting and classifying the nerve terminals, have already been reported (Minckler [12]). The method of tabulation is illustrated in table 2,

which gives the number and percentage of each type and form of *bouton* appearing on the right side of a 10 micron section through the fourth lumbar segment of the spinal cord in case 53. These figures represent total counts across the entire section, without regard to nuclear groups. A similar table has been compiled for each nuclear group in comparable sections from the individual cases. By comparing these values from cell column to cell column, from section to section and from one individual case to another, certain differences and similarities have been revealed. In comparing differences between proportions of the various *bouton* configurations, tests of significance have been applied.

RESULTS

DISTRIBUTION OF NERVE TERMINALS ACCORDING TO "TYPE"

Proportionate Distribution of "Types" of Nerve Terminals Over a Single Cell Surface.—A regional peculiarity in the types of *boutons* ending in relation to Mauthner's cell was pointed out by Bartelmez [14] and enlarged on by Bodian.[15] The latter author indicated that small terminals are especially numerous in the axon cap of Mauthner's cell, that large clubs predominate on the ventral dendrite and that still a different distribution obtains which is peculiar to the lateral dendrite. Lorente de Nó [16] postulated a general physiologic principle that synapses of different kinds have a regional distribution on a cell body and dendrites. In support of this is the nonuniformity in the number of *boutons* over a cell surface (Minckler [12]), it being found that the *bouton* density (number per hundred square microns) is extremely variable. However, the morphologic features of the nerve terminals in different regions of a cell surface do not seem to vary much in the human spinal cord.

In counts of ten selected cells in each main nuclear column of the human cord, the proportions of the morphologic types of terminals were computed for three regions—cell body, roots of dendrites and dendrites. The proportionate values of types and forms did not vary, although the absolute values were lower for the dendrites. These findings in the human cord agree with those of Hoff [4] for the spinal cord of the cat.

Proportionate Distribution of "Types" of Boutons Throughout a Single Section.—Gibson,[9] in his work on the spinal cord of the cat, assumed that the *boutons* of the dorsal and those of the ventral horn were normally of the same size. Others, however, have reported differences both in size and in configuration in nerve terminals with regard to their regional location. Hoff [4] indicated that tiny loops are especially

14. Bartelmez, C. W.: Mauthner's Cell and the Nucleus Motorius Tegmenti, J. Comp. Neurol. **25**:87-128, 1915.

15. Bodian, D.: The Structure of the Vertebrate Synapse: A Study of the Axon Endings on Mauthner's Cell and Neighboring Centers in the Goldfish, J. Comp. Neurol. **68**:117-145, 1937.

16. Lorente de Nó, R.: Studies on the Structure of the Cerebral Cortex, J. f. Psychol. u. Neurol. **45**:381-438, 1934.

numerous on the ventral horn cells of the cat. He also stated that, in general, the terminals of the dorsal horn are largest. Barr [13] found that the small end bulbs predominate in the lateral groups of the ventral horn of the spinal cord of the cat, and that terminals of intermediate size end mainly in relation to cells of the medial groups of the ventral horn and the chief sensory nucleus of the dorsal horn. In his material the large endings accompanied cells of intermediate size.

An illustration of the proportionate distribution of *bouton* types in a midthoracic section of a human spinal cord is given in table 3. These data are from

TABLE 3.—*Percentages of the Different "Types" of Terminals in the Different Cell Columns of the Midthoracic Portion of the Cord of a 71 Year Old Man*

Nuclear Column	Type 1	Type 2	Type 3	Type 4	Type 5
Dorsal sensory	51.2	24.3	0	21.9	4.8
Intermediate sensory	55.5	30.0	0	13.8	0
Ventral sensory	58.8	26.4	0	14.7	0
Intermediolateral	62.2	24.4	0	11.1	2.2
Dorsal	41.7	28.0	0	26.7	3.4
Posteromedian	47.8	25.4	0	26.7	0
Anteromedian	41.1	26.4	0	26.4	5.8

TABLE 4.—*Average Percentages of the Different "Types" of Terminals in the Different Cell Columns in the Entire Series*

Nuclear Column	Type 1	Type 2	Type 3	Type 4	Type 5
Dorsal sensory	50.42	29.36	0.74	16.97	2.56
Intermediate sensory	49.80	31.28	0.27	17.36	1.80
Ventral sensory	51.48	31.57	0.69	14.94	1.70
Intermediolateral	51.63	28.83	0.69	15.41	3.52
Dorsal	42.99	30.85	0.98	21.50	2.89
Posteromedian	47.33	30.25	1.10	19.54	2.49
Anteromedian	45.33	31.75	0.49	21.45	1.53
Posterolateral	47.31	32.06	0.49	16.56	3.57
Anterolateral	44.74	30.41	0.68	21.32	3.43
Average of totals without regard to nuclear columns	46.36	31.04	0.67	19.68	2.23

case 52, that of a man aged 71. In one-half the gray matter of this section there were 509 *boutons* adjacent to 123 cell sections.

From table 3 it is evident that type 1 *boutons* (small loops) are relatively more numerous in nuclear columns with small cells. Conversely, type 4 endings (fibrillated bulbs) are more numerous on large cells. Type 2 terminals (large loops) appear to be uniformly distributed throughout the section. Types 3 (filamented loops) and 5 (opaque or granular masses) are characteristically sparse or absent.

For purposes of generalization, the average values for the proportions of *bouton* types for the main nuclear columns in the entire series are given in table 4, which indicates that the differences noted in a single section (table 3) persist when averages from the series are considered. It seems evident, then, that small loops are relatively more numerous around small cells in the spinal cord (dorsal, intermediate and ventral sensory and internuncial columns, and the intermediolateral column), while fibrillated bulbs appear in relatively greater numbers adjacent to

the large cells (nucleus dorsalis and the somatic efferent columns). These differences may be related to differences in synaptic conduction in these various cell columns (Lorente de Nó [17]).

Distribution of "Types" of Nerve Terminals in Different Regions of the Same Spinal Cord.—Illustrations of distribution of types of terminals in different regions of the same cord are presented in table 5.

Case 53 (table 2) is used for comparison of the right and the left side of the same section (fourth lumbar segment) and of this lumbar section with one through the midthoracic region. On the right side of the lumbar section there were 3,376 *boutons* on 821 cell sections, in the left side of the lumbar section 2,342 *boutons* on 479 cell sections and in the thoracic section (one side) 701 *boutons* on 125 cell sections.

TABLE 5.—*Comparison of the Distributions of the Different "Types" of Terminals in Different Regions of the Same Spinal Cord*

	Right Side of Fourth Lumbar Region	Left Side of Fourth Lumbar Region	Right side of Sixth Thoracic Region
Type 1	45.92%	46.24%	40.23%
Type 2	37.44	37.17	34.52
Type 3	0.72	0.62	0.43
Type 4	15.54	15.32	22.97
Type 5	0.38	0.65	1.85

TABLE 6.—*Average Percentages of "Types" of Terminals at Four Different Levels of the Spinal Cord*

	Upper Cervical	Thoracic	Cervical Enlargement	Lumbar Enlargement
Type 1	41.95	44.53	50.67	48.06
Type 2	31.64	31.03	31.14	31.58
Type 3	0.39	1.32	0.00	0.68
Type 4	26.55	20.72	15.67	17.72
Type 5	1.66	2.43	2.38	1.94

No difference in distribution of *bouton* types was evident between the right and the left side of the same section. In the thoracic section, however, there were a smaller proportion of small loops (type 1) and a greater proportion of fibrillated bulbs (type 4). A summary of the average percentage distributions of types of nerve terminals in the four main regions of the cord (cervical, cervical enlargement, thoracic and lumbar enlargement) for all sections examined in this series is presented in table 6. Case 4 was omitted from the averages for reasons to be explained later in the discussion on differences based on technic and age. For this table, 3 sections were counted in the upper cervical region, 2 in the cervical enlargement, 31 through thoracic segments and 10 through the lumbar enlargement.

From these averages it appears that sections through the enlargements of the cord contained relatively more small loops (type 1) and fewer fibrillated bulbs (type 4) than sections through the thoracic and upper cervical regions. With the conspicuous increase in the number of large motor cells in the enlargements,

17. Lorente de Nó, R.: Facilitation of Motoneurones, Am. J. Physiol. **113:** 505-523, 1935.

this finding would seem to be incompatible with the inference from tables 3 and 4 that large cells have a greater precentage of fibrillated bulbs in relation to them than have small cells. This is due to there being a larger percentage of small cells in the enlargements. With case 53 as an example, the ratio of small to large cells in the thoracic section is 2:3, while in a lumbar section it is 4:3. A comparison of the data in table 3 with the average values for similar nuclear groups in table 4 gives an idea of the variation from the average in nuclear groups in an individual case.

Distribution of "Types" of Nerve Terminals at Different Ages Without Reference to Nuclear Columns.—Wide variations in appearance, size and number of nerve terminals have been reported in different individuals of the same species. In addition to technic and autolysis age has been considered to influence materially the morphologic types of *boutons* (Lache,[18] Windle and Clark,[19] Windle,[20] Tiegs [21] and Hoff [4]). In considering the age factor, only thoracic sections will be compared because of the restrictions imposed by regional differences.

TABLE 7.—*Average Percentage Distribution of Bouton "Types" According to Age Groups*

	Type 1	Type 2	Type 3	Type 4	Type 5
Averages for youngest 4 persons.....	45.09	33.57	1.80	17.42	2.10
Averages for oldest 4 persons.....	44.25	34.21	0.26	20.15	1.01
Averages for all cases.....	44.43	31.03	1.32	20.72	2.43

In this series no *boutons* were demonstrable by the technic used with cords from persons under 9 months of age (Minckler [12]). In table 7 the average proportions of the different types of nerve terminals in cases 6, 9, 12 and 15 (age range of 18 months to 23 years) are compared with similar figures for cases 53, 54, 56 and 59 (72 to 83 years) and with the average of the entire series.

Since the results are essentially without significance, there is little variation in distribution of types which can be ascribed to age after the terminals have been well established (see, however, section on "Distribution of Forms of Nerve Terminals in Different Persons"). Case 4, in which the age limit was so near that at which nerve terminals are demonstrable, was omitted in averaging values for the 4 youngest persons. In a thoracic section in case 4 there were 76 *boutons* in relation to 77 cell sections. Of these terminals, over 90 per cent were of type 1 (small loops). The general observation that infant tissues react to silver differently than adult tissue may have been a disturbing factor in this case (Duncan [22]).

18. Lache, I. G.: Sur les boutons terminaux de la cellule nerveuse, Compt. rend. Soc. de biol. **60**:381-382, 1906.

19. Windle, W. F., and Clark, S. L.: Observations on the Histology of the Synapse, J. Comp. Neurol. **46**:153-171, 1928.

20. Windle, W. F.: Normal Behavioral Reactions of Kittens Correlated with the Post Natal Development of Nerve-Fiber Density in the Spinal Gray Matter, J. Comp. Neurol. **50**:479-504, 1930.

21. Tiegs, O. W.: A Study of the Neurofibril Structure of the Nerve Cell, J. Comp. Neurol. **52**:189-222, 1931.

22. Duncan, D.: Synaptic End Bulbs in an Infant, Anat. Rec. (supp. 3) **70**: 91, 1938.

Figure 2*A* illustrates graphically the data compiled from averages of the percentages of nerve terminal types appearing in all thoracic sections counted in this series. The dorsalmost sector represents the proportions from the dorsal, intermediate and ventral sensory and internuncial columns; the dorsomedial sector includes the data from Clarke's columns; the lateral sector represents the intermediolateral column, and the ventralmost sector is compiled from the data on both the posteromedian and the anteromedian cell groups.

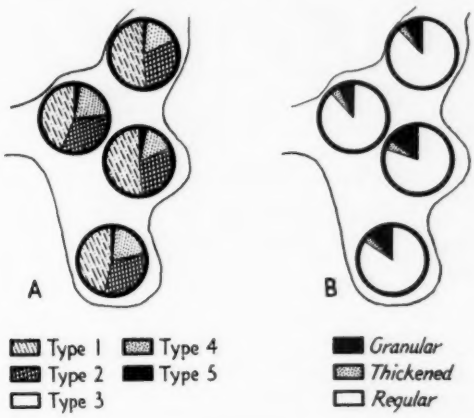

Fig. 2.—*A* represents average distributions of "types" in all thoracic sections of the series: type 1, small loops; type 2, large loops; type 3, filamented loops; type 4, fibrillated bulbs, and type 5, opaque and granular masses. *B* represents "form" distribution in a thoracic section in case 9 (patient aged 11 years).

TABLE 8.—*Number and Percentages of Nerve Terminals According to "Form" in the Different Cell Columns in Case 53*

Cell Column	Cell Sections	Number of Boutons	Regular, Percentage	Thickened, Percentage	Granular, Percentage
Dorsal sensory	80	148	75.67	4.05	20.27
Intermediate sensory	134	624	68.91	2.24	28.84
Ventral sensory	149	746	68.76	1.60	29.62
Anteromedian	46	275	74.18	2.18	23.63
Posterolateral	126	837	73.83	1.91	24.25
Central	42	282	60.99	0.00	39.01
Anterolateral	50	464	63.36	2.58	34.05
Totals and averages	821	3,376	69.40	1.95	28.64

DISTRIBUTION OF NERVE TERMINALS ACCORDING TO "FORM"

Distribution of "Forms" of Boutons in the Different Cell Columns.—The characteristic variations in the "forms" of *boutons* in the different cell columns in elderly persons are shown in table 8. In younger normal persons the proportions of granular forms appearing in block silver sections are smaller but exhibit similar variations, which are, in general, unpredictable for any nuclear group and which seem unrelated, so far as can be determined with the present data, to size or function of the cell.

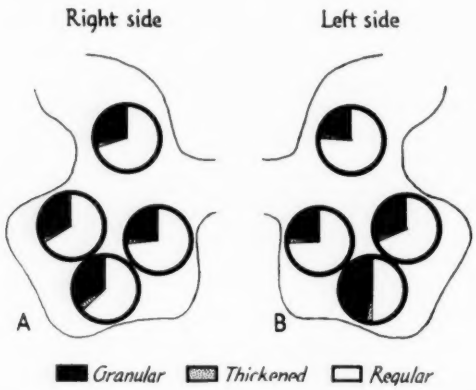

Fig. 3.—*A* represents "form" distribution on the right side of a lumbar section in case 53 (patient aged 72 years), and *B*, "form" distribution on the left side of the same section as that in *A*.

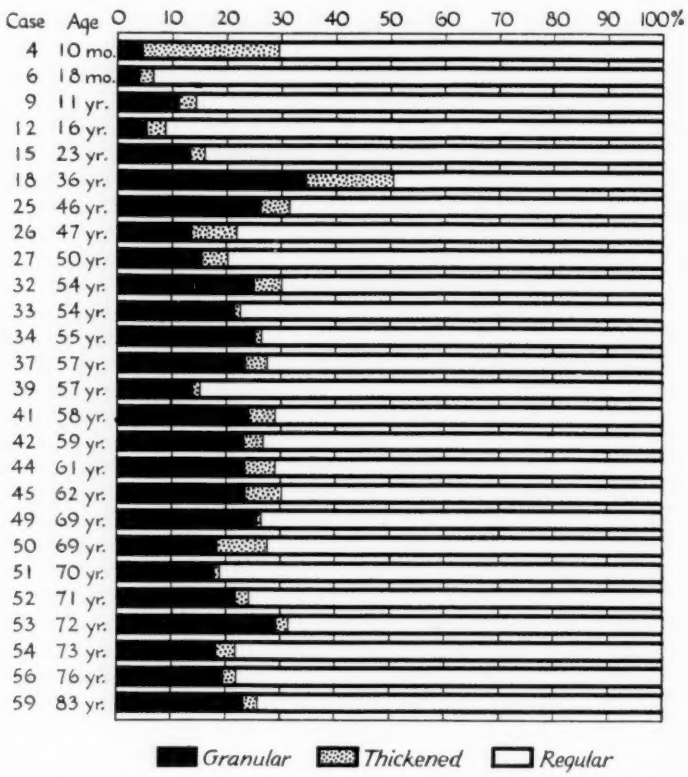

Fig. 4.—Graphic representation of the percentages of the different "forms" of endings arranged according to age.

Figures 2 *B* and 3 *A* and *B* illustrate diagrammatically the distribution of forms in the younger and older groups. The nuclear combinations illustrated in figure 2 *B* are the same as those in figure 2 *A*. In figures 3 *A* and *B* values for the sensory and internuncial columns are combined in the dorsal sector, for the anteromedian and posteromedian columns in the medial section, for the anterolateral column in the ventral sector and for the posterolateral and central columns in the lateral sector.

Case 53 (figs. 3 *A* and *B*) is of especial interest in that the left leg had been amputated five months before autopsy was performed. No difference existed in the *bouton* patterns of the posterolateral and central cell groups of the two sides, contrary to what one might suspect from the experimental work of Barnard.[10] From the analysis of the effects of amputation on human anterior horn cells by Taft,[23] it would seem that the obvious difference in the anterolateral group was unrelated to the amputation.

Distribution of "Forms" of Nerve Terminals in Different Persons.—As shown in figure 4, in which the percentages of the different forms of endings are listed in order of age, case 4 again stands out as irregular. In all the remaining cases in which the patients were 23 years of age or younger at least 85 per cent of regular forms is shown. The granular forms in the same cases represent less than 15 per cent of the total number of terminals. In only 3 of the cases of persons 46 years of age and older is there presented a proportion of regular forms of 80 per cent or over and in only 7 is there less than 20 per cent of granular forms. These data indicate that granular forms are more numerous and regular forms less numerous after 40 years of age. With the exception of case 4, which represents the lowest age at which *boutons* were demonstrable, and case 18, in which the cord was in formaldehyde for ten and a half months, the relative number of thickened forms is uniformly small at all ages.

EFFECT ON THE DISTRIBUTION OF *BOUTONS* OF TECHNIC, AUTOLYSIS AND OTHER FACTORS

Effects of Technic on Bouton Morphology.—It has been found that the technic applied within the limits given (Minckler [12]) is uncritical. Lengthened time in the silver bath tends to obscure the terminals on the cell walls, but differential counts of those which can be made out reveal no increase in thickened or granular forms. All the cords used in the present study, with one exception, were fixed in formaldehyde for a period of twelve to thirty-six hours. The single exception, that in case 18, was fixed in a dilute solution of formaldehyde U. S. P. (12 per cent) for a period of ten and a half months. The percentages of "types" of *boutons* in a thoracic section in this case differed widely from all others in the series, primarily in having a relatively large number of opaque and granular masses (type 5 terminals). From figure 4 it is evident also that the shift in *bouton* morphology is reflected in the "forms," with a conspicuous increase in thickened end bulbs and a somewhat smaller increase in granular forms. The absolute number of terminals (116 on 65 cell sections) is about one-third the usual number. Subsequent studies have shown that a period of four weeks represents roughly the time of fixation in formaldehyde beyond which optimal preparations cannot be expected.

Effect of Autolysis on Bouton Morphology.—The time between death of the subject and fixation of the cord varied in this series of cases from less than three

23. Taft, A. E.: A Comparison of Anterior Horn Cells in the Normal Spinal Cord and After Amputation, Arch. Neurol. & Psychiat. **3**:41-48 (Jan.) 1920.

to more than twenty-one hours (table 1). From the uniformity in the occurrence of types of *boutons* it is apparent that autolytic processes, operating within the limits mentioned, have little effect on the proportions of the primary morphologic groups (types) appearing in block silver sections. Also, because of the uniformly low values for thickened forms throughout the series of cords, it seems unlikely that autolysis is instrumental in increasing the silver affinity of the terminals (cf. Hoff [4]). The average time after death at which the spinal cords were fixed (approximately eight hours) being used as an arbitrary dividing point, the average proportion of granular forms appearing in sections of cords removed before that time is 21.69 per cent, as compared with 21.99 per cent in sections of cords removed after eight hours. Because of the age restrictions suggested in the section on page 53, the cases of patients under 25 years of age were excluded from these averages. It seems evident that autolysis (up to twenty-one hours) has little effect on morphologic types of *boutons* in the human spinal cord. This point is highly important in practical neuropathology, and is quite unexpected from the work on animals by Bartelmez [24] and Bodian.[25] The fact that all the bodies from which these spinal cords were taken were placed in the refrigerator immediately after death may be partly responsible for the absence of serious autolytic effect.

Other Factors Influencing Bouton Morphology.—That the appearance of granular forms is not wholly a manifestation of the aging process is evident in the nonuniform nature of their occurrence and the obvious absence of specific correlation of increasing proportions of granular forms with increasing age (fig. 4). Of the aging processes most likely to induce change in the central nervous system, arteriosclerosis would be the first suspect; but all attempts to correlate the appearance of granular forms with this arterial condition (based on grading the aorta at autopsy) have failed. Inanition (Jackson [26]), intoxications, prolonged fever and dehydration may be expected to induce observable effects in the central nervous system which might be reflected in the morphologic forms of the nerve terminals. In case 9 (fig. 4), for example, more granular forms appeared than is usual in the age group. Of possible importance in this connection is a history of prolonged severe terminal illness with acute systemic infection and numerous complications. In addition, the nature of the agonal period may be of some importance. These factors are difficult to analyze, since many occur conjointly in the same case, and frequently the history is incomplete with respect to these specific points. The material at hand is not adequate for full consideration of these factors in relation to *bouton* morphology. It is believed, however, that the data from cases of neuropathologic disorders, to be reported later, will be of some value in explaining certain phases of this problem.

SUMMARY

1. Counts of the nerve terminals of the human spinal cord in block silver sections show that proportions of the various morphologic "types" of *boutons* (small loops, large loops, filamented loops, fibrillated bulbs and opaque or granular masses) remain about the same regardless of

24. Bartelmez, C. W.: The Morphology of the Synapse in Vertebrates, Arch. Neurol. & Psychiat. **4**:122-126 (July) 1920.

25. Bodian, D.: The Staining of Paraffin Sections of Nervous Tissues with Activated Protargol: The Role of Fixatives, Anat. Rec. **69**:153-162, 1937.

26. Jackson, C. M.: Inanition and Malnutrition, Philadelphia, P. Blakiston's Son & Co., 1925, pp. 193-197.

age, provided certain limitations in technic are observed and the same regions, including similar nuclear groups, are compared.

2. The different types of terminals are found in about the same relative numbers on different parts of the nerve cell.

3. Small loops appear in relatively greater number adjacent to the smaller cells of the cord (dorsal, intermediate and ventral sensory and internuncial columns, and the intermediolateral column), while fibrillated bulbs are more numerous on larger cells (nucleus dorsalis and the somatic efferent columns).

4. The proportions of the three "forms" of nerve terminals (regular, thickened and granular) show numerous variations from case to case and from cell column to cell column in a single case. These variations occur in persons whose symptoms had indicated no involvement of the central nervous system.

5. In general, granular forms are relatively more numerous in persons of middle age or older.

6. Technic, such as prolonged fixation in formaldehyde, may be responsible for the appearance of thickened forms, and possibly for some of the granular forms of *boutons* in block silver sections.

7. Autolytic processes, operating up to twenty-one hours, appear to be of little importance in producing changes in *bouton* morphology demonstrable with the technic used.

CHANGES IN THE BRAIN IN ALCOHOLISM

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The problem of the misuse of alcohol and its effects on the human organism is an old one. The interest of neurologists in the subject was suddenly focused by the publication of Wernicke's [1] paper in 1881. He described the cases of 3 patients who died and were found, post mortem, to have punctate hemorrhages surrounded by fat granule corpuscles about the third and fourth ventricles and the midbrain. Clinically, the patients had shown paralysis of the ocular muscles, ataxic gait and disturbance of consciousness, ending in coma. There were also changes in the optic disks. He expressed the belief that the condition was a disease entity. It has been called, even to the present, Wernicke's disease, or polioencephalitis superior alcoholica. In his first case, however, the disease was not due to alcoholism. The patient, a woman aged 20, had been poisoned with sulfuric acid and later suffered from vomiting; she died about twelve days after the onset of cerebral symptoms. In addition to the changes in the brain there was chronic ulcerative gastritis, with stenosis of the pylorus.

Ecker and Woltman [2] recently asked the question: "Is nutritional deficiency the basis of Wernicke's disease?" They reported the case of a woman aged 50 who had vomited daily for five weeks before she was seen by them. While the patient was under observation, there developed Wernicke's syndrome, with retinal hemorrhages, afebrile tachycardia and continual movements of the lower limbs. She continued to vomit in spite of treatment and died in about a month. Presumably

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1. Wernicke, C.: Die acute hämorrhagische Polioencephalitis superior, in Lehrbuch der Gehirnkrankheiten, Berlin, T. Fischer, 1881, vol. 2, p. 229.

2. Ecker, A. D., and Woltman, H. W.: Is Nutritional Deficiency the Basis of Wernicke's Disease? J. A. M. A. **112**:1794 (May 6) 1939.

she was not alcoholic. Petechial hemorrhages could be seen with the naked eye in the mamillary bodies and in the posterior corpora quadrigemina. Petechial hemorrhages were also seen in the skin and lungs, and there was atrophy of the liver and of the gastric and intestinal mucosa. Advanced chromatolysis was present in the nuclei of the nerves supplying the ocular muscles and in the thalamus. The authors expressed the belief that this disease picture was due to loss of essential secretions or to a diet deficient in vitamins. The tachycardia, in their opinion, was caused by a deficiency in vitamin B, and the retinal hemorrhages were due to deficiency of vitamins.

There is a recent tendency to ascribe alcoholic polyneuritis entirely to associated vitamin B deficiency rather than to the toxic effect of the alcohol. For example, Jolliffe and Colbert [3] concluded that alcohol per se is not the cause of polyneuritis in the alcoholic addict, but that vitamin B deficiency is the etiologic factor. They studied 28 alcoholic persons with uncomplicated polyneuritis: some of them were given diets containing slightly inadequate quantities of vitamin B, and others a diet containing two or four times the estimated vitamin B requirement. Those receiving inadequate amounts of vitamin B showed no improvement in the peripheral neuritis during a period of one month. Two of these patients were then given crystalline vitamin B_1 intravenously, with dramatic response in 1 case and a good response in the other. Patients given vitamin B in approximately twice the predicted requirement showed improvement, but not as rapidly or to the same degree as those receiving four times the vitamin B requirement. More recently, in certain cases of alcoholic encephalopathy the causal factor has been described as a deficiency in nicotinic acid by Jolliffe, Bowman, Rosenblum and Fein.[4] These authors observed 150 cases of an "encephalopathic syndrome" characterized by clouding of consciousness, cogwheel rigidities and uncontrollable grasping and sucking reflexes, which may or may not be associated with polyneuritis, with pellagra or with the oculomotor signs of "central neuritis." They found that when patients with this syndrome were treated by means of hydration or hydration plus thiamine hydrochloride they almost always died. When such patients were treated with hydration plus nicotinic acid there was a marked drop in the mortality. They therefore concluded that the syndrome is due to deficiency in nicotinic acid and that the pathologic changes are reversible in cases in which the disease has not advanced too far. This conclusion is in accord with the paucity of findings

3. Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107**:642 (Aug. 29) 1936.

4. Jolliffe, N.; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy, J. A. M. A. **114**:307 (Jan. 27) 1940.

reported in our own study of the changes in the brain in cases of alcoholic encephalopathy.

Experimental studies on animals deprived of vitamin B date back to the old laboratory experiment of feeding chickens polished rice, with production of peripheral neuritis. Grinker and Kandel [5] were unable to demonstrate significant lesions of the central nervous system in rats deprived of vitamin B complex. They stated that long-standing severe deficiencies in vitamins B_1, G (B_2) and B complex in rats cause no clinical symptoms or histologic changes in the central nervous system of a degenerative character, save for mild, nonspecific alterations in the ganglion cells and blood vessels.

Prickett [6] observed no significant changes in the peripheral nervous system of rats deprived of vitamin B (heat-labile factor) but with an adequate amount of vitamin G in the diet. However, he observed hemorrhages, together with cellular changes, in Deiters' nucleus and other vestibular nuclei and in the nucleus of the tractus solitarius in 75 per cent of the animals.

Church [7] found clinically that rats deprived of vitamin B_1 showed ataxia, changes in muscle tone, disturbance of equilibrium and hyperexcitability, with tremors and weakness at times. He expressed the belief that true convulsions and paralysis did not occur in association with beriberi in these animals. He concluded that the chief neurologic manifestations of beriberi in the rat could be accounted for on the basis of lesions in the vestibular nuclei. He observed hemorrhages in this region, but considered them secondary to other tissue changes resulting from specific lack of vitamin B_1.

Gildea, Castle, Gildea and Cobb [8] observed areas of loss of myelin in the spinal cord of animals deprived of vitamin B, which resembled the picture seen in subacute combined degeneration of the spinal cord in man.

Davison and Stone,[9] in rats deprived of vitamin B_1 or vitamins B_1 and G (B_2), observed the clinical picture of dragging and paralysis of the extremities, disturbance of equilibrium, priapism, convulsions and

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5. Grinker, R. R., and Kandel, E.: Experimental Vitamin (A, B_1, B_2 and B Complex) Deficiency, Arch. Neurol. & Psychiat. **30**:1287 (Dec.) 1933.

6. Prickett, C. O.: The Effect of a Deficiency of Vitamin B_1 upon the Central and Peripheral Nervous System of the Rat, Am. J. Physiol. **107**:459, 1934.

7. Church, C. F.: Nervous System in Experimental Beri-Beri, Am. J. Physiol. **111**:660, 1935.

8. Gildea, M. C. L.; Castle, W. B.; Gildea, E. F., and Cobb, S.: Neuropathology of Experimental Vitamin Deficiency (Report of Four Series of Dogs Maintained on Diets Deficient in B Vitamins), Am. J. Path. **11**:669, 1935.

9. Davison, C., and Stone, L.: Lesions of the Nervous System in Vitamin B Deficiency, Arch. Path. **23**:207 (Feb.) 1937.

tonic retraction of the head. The pathologic changes were disintegration of myelin sheaths of peripheral nerves and vacuoles and liquefaction necrosis in ganglion cells of the mesencephalon, metencephalon and anterior horn cells of the spinal cord. Hemorrhages with changes in ganglion and glia cells of the mesencephalon were also seen in the rats with convulsions.

Alexander, Pijoan and Myerson,[10] in a study on pigeons and guinea pigs, found that the clinical symptoms in pigeons with beriberi (ataxia, convulsions, localized pareses) were specific for vitamin B_1 deficiency and that the clinical picture was different from the generalized weakness of vitamin G (B_2) deficiency or of starvation. They stated also that the pathologic phenomena were less specific than the clinical syndrome. The lesions of Wernicke's disease also can be produced in pigeons with vitamin B_1 deficiency. More recently, Alexander,[11] in a paper on Wernicke's disease, showed the identity of lesions produced experimentally in pigeons by B_1 avitaminosis with hemorrhagic polioencephalitis occurring in association with chronic alcoholism in man. According to this paper, not only the hemorrhages but the changes in blood vessels produced experimentally in pigeons are apparently similar to those observed in cases of chronic alcoholism in man. The blood vessels showed varicose deformities, degeneration of the vascular walls and intense proliferation of endothelial and adventitial cells. Severe changes in the nerve cells were also found in these pigeons.

With regard to the pathologic picture observed in chronic alcoholism and other conditions associated with deficiency states in man, one finds, after Wernicke's paper, an article by Meyer[12] on central neuritis, published in 1901. Meyer found this alteration in cases of peculiar forms or end stages of "depressive disorders, near or after the climacteric period, alcoholico-senile and alcoholico-phthisical cachectic states, idiocy, and perhaps also general paralysis. . . . Ordinary infectious and cachectic states do not, however, appear to form an important link in the causes."

Singer and Pollock,[13] in 1913, studied 14 cases of pellagra, with necropsies. It is not stated whether or not any of the patients were alcoholic, but 5 were said to have senile dementia and 4 had dementia praecox. In this paper, much of the older literature was cited and the authors concluded, among other things, that the acute attack of pellagra

10. Alexander, L.; Pijoan, M., and Myerson, A.: Beri-Beri and Scurvy, Tr. Am. Neurol. A. **64**:135, 1938.

11. Alexander, L.: Wernicke's Disease, Am. J. Path. **16**:61, 1940.

12. Meyer, A.: Parenchymatous Systemic Degenerations Mainly in the Central Nervous System, Brain **24**:47, 1901.

13. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. **11**:565 (June) 1913.

gives rise to "central neuritis," and that none of the changes are characteristic of this particular form of intoxication, it being assumed, apparently, that pellagra is an intoxication.

Gamper [14] studied cases of chronic alcoholism with Korsakoff's psychosis. He reported, among other changes, proliferation of the endothelial and muscular coats of blood vessels, neuroglial overgrowth and secondary destruction in the inferior quadrigeminal and mamillary bodies.

Neubürger,[15] in a survey of changes in the brain associated with misuse of alcohol, came to the conclusion that alcohol is not necessarily the only cause of these changes.

Langworthy [16] studied a case of pellagra with changes in the brain. The case was that of a white woman aged 22 who had had tuberculous ulcers of the intestine and severe diarrhea and vomiting, as well as dermatitis, for a number of months. Necropsy showed that the heart and uterus were small, with some hemorrhages in the heart muscle. The spinal cord contained fat in the spinocerebellar tracts and lateral columns, both free and in phagocytes. There was an increase in lipoid pigment in all the nerve cells, but this was most marked in the cells of the autonomic and sensory ganglia.

Carmichael and Stern [17] examined the pathologic changes in 5 cases of Korsakoff's syndrome. There was an excessive deposit of lipochrome in all nerve cells, in the neuroglia and microglia cells and around the blood vessels in the prefrontal and motor cortex, with acute chromatolysis in the larger nerve cells, especially the Betz cells. They noted the similarity in appearance of the changes in the nerve cells in Korsakoff's syndrome and those in pellagra.

Bender and Schilder [18] studied 7 cases of alcoholic encephalopathy in which necropsy was performed. They concluded that the pathologic changes in the nervous system always occur in parts adjacent to spinal fluid spaces. In other words, the lesion is always marginal. Furthermore, the lesion is usually more severe where the spinal fluid flows least freely. They suggested that the spinal fluid contains a noxious agent

14. Gamper, E.: Zur Frage der Polioencephalitis hemorrhagica der chronischen Alkoholiker, Deutsche Ztschr. f. Nervenh. **102**:122, 1928.

15. Neubürger, K.: Ueber Hirnveränderungen nach Alkoholmissbrauch (unter Berücksichtigung einiger Fälle von Wernickescher Krankheit mit anderer Ätiologie), Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:159, 1931.

16. Langworthy, O. R.: Lesions of the Central Nervous System Characteristic of Pellagra, Brain **54**:291, 1931.

17. Carmichael, E. A., and Stern, R. O.: Korsakoff's Syndrome: Its Histopathology, Brain **54**:189, 1931.

18. Bender, L., and Schilder, P.: Encephalopathia Alcoholica, Arch. Neurol. & Psychiat. **29**:990 (May) 1933.

responsible for the lesions. These authors observed gliosis in the cerebral cortex in the first cortical layer and "cytoplastic gliosis" in the second and third layers, together with swelling of the microglia and oligodendroglia. In the cerebellum they noted that the lesion was patchy, with glial scarring and retraction of the outer layer, loss of Purkinje cells and invasion of the "corpuscular layer" by glia cells. They expressed the belief that the marginal gliosis is the explanation for much of the involvement of the optic nerve. The ependymal reaction is the most pronounced and characteristic part of the glial change, according to these authors. It is both reactive and invasive and tends to narrow the lumen of the ventricles and aqueduct.

The second principle stressed by Bender and Schilder is that, aside from the ependymal and marginal gliosis, the lesion seems to be primarily vascular. They stated that the hemorrhages are characteristic and that capillary budding is conspicuous, with proliferation of the endothelial and adventitial layers. The vascular lesions have in general the same distribution as the glial changes, but invade more deeply. To some extent they are found on all surfaces of the central nervous system, but are most marked within the brain stem along the ventricles.

The last principle stressed is a tendency toward a specific electivity for gray masses, especially for the vegetative gray masses that surround the ventricles. The most severe lesions are found in the floor of the fourth ventricle, including the nuclei of the eighth to the twelfth nerve, and in the periaqueductal gray masses, including the nuclei of the nerves to the ocular muscles. The authors expressed the belief that the lesion in the mamillary bodies invades from the periphery, with the center of the bodies free in some cases. These studies, they stated, show a close correlation between the lesions and the clinical picture. The five clinical groups described show a corresponding difference in the anatomic localization and the type of the lesion.

Warner [19] studied 7 cases of chronic alcoholism, in 1 of which there was a typical Wernicke syndrome and in 2 a Korsakoff syndrome; in the others the condition was diagnosed as chronic alcoholism with delirium. He contended that the localization of the pathologic changes was not constant, a view which is in contrast to the observations of Neubürger, Bender and Schilder and others. He concluded that the histopathologic changes in chronic alcoholism show great variation, both in character and distribution, and that there seems to be no correspondence between the severity of the clinical symptoms and the degree of the corresponding changes in the brain.

19. Warner, F. J.: Brain Changes in Chronic Alcoholism, J. Nerv. & Ment. Dis. **80**:629, 1934.

Berner [20] maintained that the vessels of the floor of the fourth ventricle are more disposed to diapedesis than those of the rest of the brain, not only in acute intoxication due to methyl alcohol but also in conditions not related to alcohol intoxication.

Neubürger [21] reported 14 cases in which there was no history of alcoholism and in which cirrhosis of the liver was not a factor, but in which there was evidence of Wernicke's syndrome, with corresponding pathologic changes in the mamillary bodies, paraventricular ring hemorrhages, glial proliferation and proliferation of blood vessels. In 9 of the cases there was carcinoma—of the stomach, in 7 cases, of the rectum in 1 case and of the pancreas in 1 case; in 1 case there was a melanosarcoma, and in 1 chronic atrophic gastritis. Anemia was present in all of the author's cases, and he expressed the belief that a toxic substance might be liberated from the tumor in such cases, or from some other source in other cases.

Vonderahe [22] studied 14 cases of peptic ulcer, with necropsy; 3 of the patients were alcoholic. He observed hemorrhages in the anterior portion of the hypothalamus, the gray matter of the third ventricle, the superior portion of the nucleus paraventricularis and elsewhere. He noted severe retrograde changes in the cells of many of these nuclei. There were hemorrhages also in the thalamus and in the dorsal motor nucleus of the vagus nerve, but nowhere else in the medulla. He concluded that the rapid pulse rate and increased sweating in cases of gastric ulcer are due to hemorrhage in the dorsal motor nucleus of the vagus.

Most of these studies, experimental and clinical, tend to show that alcohol in itself is not the cause of the encephalopathic and peripheral neuritic syndrome associated with chronic alcoholism. The studies particularly of Jolliffe and Colbert [3]; of Jolliffe, Bowman, Rosenblum and Fein,[4] and, most recently, of Cleckley, Sydenstricker and Geeslin [23] have tended to show by therapeutic tests that these diseases of the nervous system are not irreversible and can be cured in a large percentage of cases if the appropriate vitamins in which the patient is deficient are

20. Berner, O.: Ueber Blutungen im hintersten Teil des Hirnstammes bei Vergiftungen und Entzündungen, verglichen mit solchen nach Trauma, Virchows Arch. f. path. Anat. **296**:636, 1936.

21. Neubürger, K.: Ueber die nichtalkoholischer Wernickesche Krankheit insbesondere über ihr Vorkommen beim Krebsleiden, Virchows Arch. f. path. Anat. **68**:298, 1936.

22. Vonderahe, A. R.: Histopathologic Changes in the Nervous System in Peptic Ulcer, Tr. Am. Neurol. A. **64**:24-28, 1938.

23. Cleckley, H. M.; Sydenstricker, V. P., and Geeslin, L. E.: Nicotinic Acid in the Treatment of Atypical Psychotic States Associated with Malnutrition, J. A. M. A. **112**:2107 (May 27) 1939.

given him in adequate amounts. This is a fitting clamix to the work of Goldberger and Wheeler,[24] who, in 1920, were able to show that pellagra can be produced in the human subject by means of a deficient diet and is not due to infection or intoxication from spoiled maize, as had been so long contended.

This theory of the pathogenesis of alcoholic encephalopathy leaves alcohol practically blameless. It has been found, however, by Jolliffe and his co-workers [25] that some other forms of alcoholic psychosis (for example, alcoholic encephalopathy with delirium or with catatonia) are not cured by adequate vitamin therapy; hence one must consider what part alcohol does play in some of these conditions. An adequate discussion of this problem is beyond the scope of the present article; it is known, however, that alcohol makes one drunk and causes one to behave in a foolish, if not a psychotic, manner, no matter how many vitamins and calories one may consume. Alcohol, for example, blots out memory for recent events. We believe that in some way also alcohol paves the way for other factors to enter the body as pathogenic agents and that alcohol sensitizes the body to infections (focal and otherwise) and predisposes to cerebral hemorrhage (Howe [26]).

The relation of alcoholic consumption to cirrhosis of the liver is an interesting question which is still unsolved. In this connection, the recent experiments of Page, Graef and Sweet [27] are important. These investigators found that in certain hypophysectomized dogs nodular hepatic cirrhosis developed in from nine months to two and a half years after operation. This, of course, raises the question whether changes in the brain (the hypophysis or its stalk, or possibly the hypothalamus) may not cause the cirrhosis sometimes seen in persons who consume large amounts of alcohol and are probably deficient in vitamins. Up to the present, we have been led by the experiments of Weil [28] and others to believe that changes in the liver had a profound effect on the brain, rather than vice versa.

MATERIAL AND METHODS

In the present study, we have examined the clinical histories, the general autopsy observations and the changes in the brain in 44 cases of chronic alcoholism. Forty cases were from the Psychiatric Division of Bellevue Hospital. Dr. Karl Bowman,

24. Goldberger, J., and Wheeler: Experimental Production of Pellagra in the Human Subject by Means of Diet, Hygienic Laboratory Bulletin 120, United States Treasury Department, Public Health Service, 1920.

25. Jolliffe, N.: Personal communication to the authors.

26. Howe, H. S.: Personal communication to the authors.

27. Page, I. H.; Graef, I., and Sweet, J. E.: The Development of Hepatic Cirrhosis Following Hypophysectomy, read at the meeting of the American Association of Pathologists and Bacteriologists, Richmond, Va., April 7, 1939.

28. Weil, A.: A Textbook of Neuropathology, Philadelphia, Lea & Febiger, 1933, p. 198.

director of the department, has allowed us to use the clinical observations made by his staff. Four cases came from the Third Medical Division, Dr. William Tillett, director.

Changes in organs other than the nervous system were recorded by various interns in the department of pathology, under the immediate supervision of the respective assistant pathologists and under the general direction of Dr. Douglas Symmers.

Fig. 1.—Alcoholic encephalopathy. Section through the mamillary bodies (Masson's trichrome stain) showing a few very small hemorrhages, particularly in the upper half of each body.

The material was usually fixed in a solution of formaldehyde and sodium bromide. Sections were taken in most cases from the superior frontal gyrus, the midbrain, the medulla and the cerebellum, through the third ventricle at the level of the mamillary bodies and through the pons, the corpus callosum and, in a few instances, the spinal cord. The optic nerves were examined in 38 cases, the nucleus of the third nerve in 27 and the region of the vestibular nuclei in 16.

Masson's trichrome stain was chiefly employed with pyroxylin sections for demonstration of petechial hemorrhages, arachnoiditis and changes in blood vessels.

The Nissl stain was frequently used for changes in nerve cells, although the nerve cells were well stained by the trichrome stain also. The Loyez method was used as a stain for myelin in the optic nerves, spinal cord and brain. Frozen sections were stained for fat by Hortega's nuclear stain and sudan III, by hematoxylin and sudan III or by scarlet red. Marchi stains were made in some cases. Frozen sections were stained by Hortega's silver carbonate method for astrocytes and for microglia.

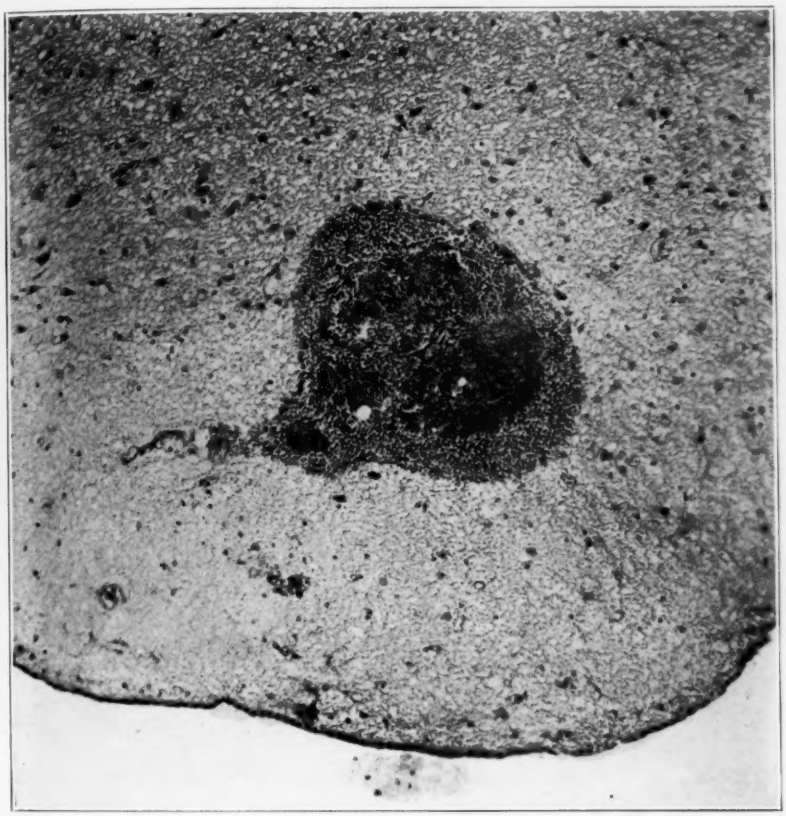

Fig. 2.—Psychosis with somatic disease due to alcohol. Section through the wall of the third ventricle (Masson's trichrome stain) showing a perivenous hemorrhage near the wall of the third ventricle. This section also shows normal ependyma lining the ventricle.

RESULTS

In the 43 original cases, there were 29 males and 14 females. Three of the males were Negroes; all other patients were white. The average age for the group was 47, and the average stay in the hospital was eleven days. The average blood pressure was 144 systolic and 88 diastolic; the average percentage of hemoglobin was 74, and the average nonprotein nitrogen content of the blood was 42 mg. per hundred cubic centimeters. Cirrhosis of the liver, usually early,

was described in 11 cases. Severe, moderate or mild fatty change in the liver was recorded in 38 cases. In 4 cases there was acute splenitis and in 1 case septic splenitis. In 3 cases acute or hemorrhagic pancreatitis was present (this, Dr. Foster Kennedy said, used, at a hospital in Belfast, to be called "Saturday night disease" and was frequently observed in cases of alcoholism). In 12 cases submucosal hemorrhages in the stomach or duodenum were present; in 1 there was multiple perforation of the intestine and in 1 ruptured duodenal ulcer. In 33 cases some form of heart disease was presented—in most instances coronary sclerosis. In 33 cases, likewise,

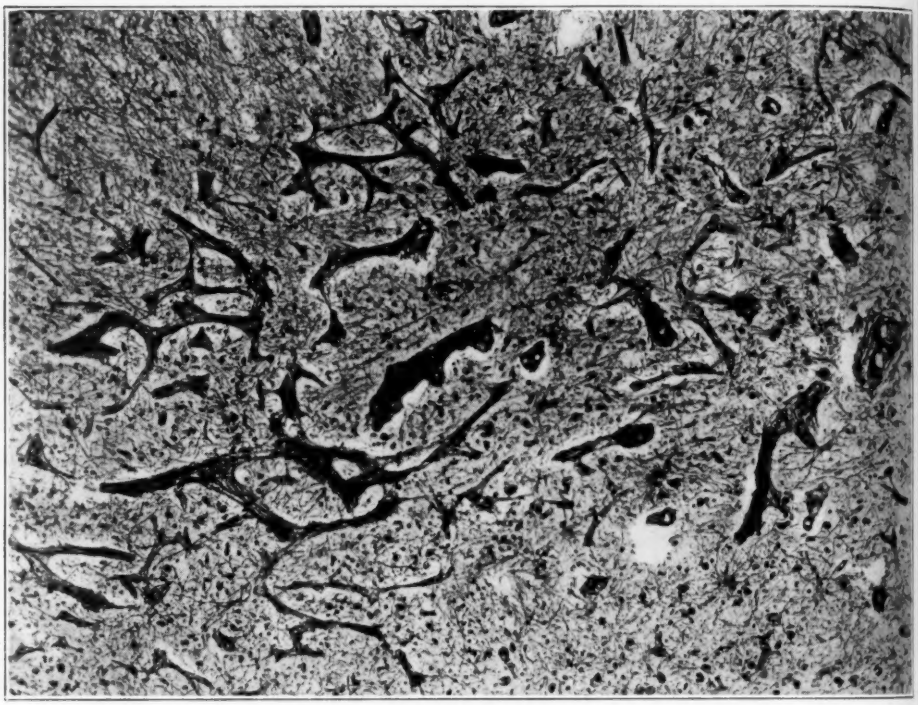

Fig. 3.—Alcoholic encephalopathy. High power view of part of the mamillary body (frozen section; silver carbonate stain), showing increase in the number of blood vessels, with fibrous thickening of the vessel wall.

there was a pathologic change in the aorta. In 12 cases the kidneys were normal. In 6 cases there was some type of sepsis, and in 4 others septicemia. In 7 cases there was a history of one or more convulsions, and in 1 of these there was epilepsy of long standing. In 6 cases there was tuberculosis of the lungs or bronchial lymph nodes. In 10 cases evidence of avitaminosis other than signs of peripheral neuritis was presented. There were only 2 cases of subdural hematoma.

In 22 cases the clinical diagnosis was alcoholic encephalopathy. Since it is impossible to present all the data collected in the form of tables, we chose only these cases for presentation in this manner, in order that we might see whether there is any correlation between the anatomic distribution of lesions and the

TABLE 1.—*Psychiatric Symptoms in Twenty-Two Cases of Alcoholic Encephalopathy*

Case number...	1	2	3	4	5	N* 6	7	8	N 9	10	11	N 12	13	N 14	15	N 16	N 17	N 18	19	20	21	N 22
Clouding of consciousness..	+	..	..	..	+	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Apathy.....	+	..	+	+	..	+	..	+	+	..	..	..	+	..	+	..	+	..	..	..	..	..
Dulness and retardation.....	+	..	+	+	..	+	..	+	+	..	..	..	+	..	+	..	+	+	..	..	+	..
Confusion.....	+	+	+	+	+	+	+	+	..	..	..	..	..	..	+	+	+	+	+	+	+	+
Disorientation..	+	+	+	+	..	+	..	+	..	..	..	+	..	..	+	+	+	+	+	+	+	+
Incoherence.....	..	..	..	..	..	+	..	+	+	+	..	..	..	..	..	..	..	+	..	..	..	+
Unintelligible mumbling.....	..	..	..	+	..	..	..	..	+	..	+	..	..	..	+	..	..	+	+	..	..	..
Semicoma.....	+	..	..	..	..	+	+	+	..	..	+	..	+	+	..	..	..	+	..	..	..	..
Hallucinations.	..	+	..	..	+	+	..	+	+	..	..	+	..	+	+	+	+	+	+	+	+	+
Delirium.....	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..
Memory defects	..	+	+	+	..	..	..	+	..	..	..	..	..	..	..	..	..	+	+	..	+	..
Confabulation.	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	+	..
Deterioration...	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Catatonia.....	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..
Tremulousness.	+	+	..	..	+	..	..	+	+	..	+	+	..	..	..	..	+	..	..	+	+	..
Restlessness....	+	..	..	..	+	..	+	+	..	..	..	..	..	..	+	+	..	..	+	..	..	+
Agitation; excitement.....	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+
Resistiveness...	..	+	..	..	..	+	+	..	..	..	..	..	..	..	..	..	+	..	..	..	..	+

* In this table, and in the accompanying tables, N indicates encephalopathy due to nicotinic acid deficiency.

TABLE 2.—*Neurologic Signs in Twenty-Two Cases of Alcoholic Encephalopathy*

Case number...	1	2	3	4	5	N 6	7	8	N 9	10	11	N 12	13	N 14	15	N 16	N 17	N 18	10	20	21	N 22
Unequal pupils.	..	..	..	+	..	+	..	..	..	+	..	..	+	..	..	..	+	..	+	+	+	..
Pupils fixed to light.....	..	..	..	..	..	..	+	..	..	..	+	+	+	+	..	..	..	..	..	+	..	..
Pupils sluggish to light.....	..	+	..	+	..	..	..	..	..	..	..	..	..	..	+	..	..	..	+	..	..	+
Paralysis of eye muscles.....	+	..	+	+	..	+	..	..	..	..	..	+	..	..	..	..	..	+	..	..	..	+
Nystagmus.....	+	+	+	..	..	+	..	+	..	..	..	+	..	..	+	..	..	..	+	..	..	..
Tenderness of eyeballs.....	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..	..	+	..	+	..	..
Facial weakness	..	..	..	+	+	..	..	+	..	..	..	..	..	..	..	..	..	+	..	..	..	+
Dysarthria.....	..	.	..	+	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	+	..	..
Rigidity of neck	..	+	..	..	+	..	..	+	+	..	+	..	..	..	+	..	..	..	..	+	..	..
Absence of knee jerks.....	..	+	+	..	..	..	+	..	..	+	..	+	..	+	..	..	+	..	+	..	..	..
Absence of ankle jerks.....	..	+	+	..	+	..	..	..	+	+	..	+	..	+	+	+	+	..	+	..	..	+
Babinski sign...	..	..	..	..	..	..	..	+	+	+	..	+	..	..	..	..	..	..	..	..	..	..
Hyperactive reflexes.....	..	..	+	..	..	..	..	+	..	..	..	..	..	..	..	..	..	+	..	..	..	..
Grasping reflex	..	+	..	+	+	+	..	..	+	+	..	..	..	+	+	+	+	+	+	+	..	+
Sucking reflex..	..	+	..	+	+	+	..	..	..	+	..	+	..	+	+	+	+	+	..	+	..	+
Changing rigidities.....	..	+	..	+	+	+	..	..	..	..	..	..	..	+	+	+	+	..	..	..	..	+
Athetoid movements.....	..	+	..	..	..	..	..	..	..	+	..	..	..	+	..	..	..	..	..	..	..	..
Solar hyperesthesia.....	..	+	..	..	+	..	..	..	..	+	..	..	..	+	..	+	+	..	..	+	..	..
Tenderness of calf muscles...	..	..	..	..	+	..	..	..	..	+	..	..	..	+	+	+	+	..	+	..	..	..
Sensory loss....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	+	..	..	..
Convulsions....	..	..	..	..	..	+	..	..	..	..	+	..	..	+	..	..	..	+	..	..	..	..
Avitaminosis...	+	+	+	..	+	+	..	..	..	+	..	+	..	+	+	+	+	..	+	+	+	..

clinical picture and between the changes in the brain and the general pathologic condition. Eight cases in this group (designated by *N* over the case number) were considered by Dr. Norman Jolliffe to be those of encephalopathy due to

TABLE 3.—*General Pathologic Changes in Twenty-Two Cases of Alcoholic Encephalopathy*

Case number...	1	2	3	4	5	N 6	7	8	N 9	10	11	N 12	13	N 14	15	N 16	N 17	N 18	19	20	21	N 22
Cirrhosis of liver	..	+	..	..	..	..	+	..	..	..	..	..	..	..	+	..	..	..	+	..	..	+
Fatty change in liver	+	+	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Disease of kidneys	+	..	..	+	..	+	+	+	..	..	+	..	+	..	+	+	+	+	+	..	+	..
Atherosclerosis of aorta	+	+	..	+	..	+	+	+	+	+	+	..	..	+	+	+	+	+	+	+	+	+
Heart disease	..	..	+	..	..	..	..	+	..	+	+	..	..	+	+	+	+	+	+	+	+	+
Pathologic changes in gastrointestinal tract	..	..	..	..	+	+	+	..	..	+	+	..	..	+	..	..	..	..	..	+	..	..
Disease of pancreas	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	..	..	+	..	..	..	..
Septicemia	..	..	+	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..
Pneumonia	+	+	..	..	+	..	..	+	..	+	+	..	..	..	..	..	..	+	+	..	+	+
Syphilis	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..
Tuberculosis	..	..	..	+	..	..	+	..	+	+	..	..	..	+	..	+	+	..	..	..	+	+
Hemorrhage other than cerebral	+	..	..	..	+	+	+	..	..	+	+	..	+	+	..	..	+	..	..	+	..	..
Pellagra, scurvy, etc.	+	..	..	..	..	+	..	..	..	..	..	+	..	..	..	+	..	..	..	..	+	..

TABLE 4.—*Pathologic Changes in the Nervous System in Twenty-Two Cases of Alcoholic Encephalopathy*

Case number...	1	2	3	4	5	N 6	7	8	N 9	10	11	N 12	13	N 14	15	N 16	N 17	N 18	19	20	21	N 22
Arachnoiditis	+	+	+	+	+	+	+	+	+	+	+	..	..	+	+	+	+	+	+	+	+	+
Hemorrhages (petechial)	+	+	+	..	+	+	..	+	+	+	+	..	..	..	+	+	+	+	+	+	..	+
Edema (microscopic)	+	+	..	+	+	+	+	+	..	+	..	+	+	+	+	+	+	+	+	..	+	+
Increase of vascularity in mamillary bodies	..	..	..	..	..	..	+	..	..	..	..	+	+	..	+	..	..	..	+	..	..	..
Increase of vascularity elsewhere	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Ependymitis	+	+	..	+	..	..	..	..	+	+	..	..	..	..	..	..	..	..	..	+	..	..
Gliosis	..	..	..	+	..	+	..	..	+	+	..	..	+	..	+	+	+	..	..	..	..	..
Pathologic changes in optic nerves	..	..	..	..	..	..	..	..	+	+	..	..	..	..	+	..	+	..	..	..	+	..
Increase of lipochrome in nerve cells	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..	+	..
Other changes in nerve cells	..	+	..	+	+	..	+	..	..	..	..	+	+	..	..	..	+	+	..	+	+	+
Arteriosclerosis	+	..	..	+	..	..	+	+	+	..	+	..	..	+	+	+	+	+	..	..	..	+
Subdural or other gross hemorrhages	+	..	..	..	+	..	..	..	..	..	+	..	+	..	..	..	..	+	..	..	..	+

nicotinic acid deficiency. In 3 cases the diagnosis was alcoholic psychosis with somatic disease; in 6, alcoholic psychosis with delirium; in 2, Korsakoff's psychosis, and in 8, acute and chronic alcoholism; in 2 cases the diagnosis was

unclassified psychosis due to alcohol. In 1 case (that of a female) the condition was diagnosed clinically as acute encephalitis in the medical service, but was discovered to be alcoholic encephalopathy.

Table 1 shows the psychiatric symptoms. Some alteration of consciousness, variously described as clouding, apathy, dulness, confusion or semicoma, was present in all cases. Sixteen patients were described as confused, and 15 were disoriented. Fifteen had hallucinations, and 10 had tremors. Only 2 had delirium, and only 2 presented catatonic features. Excitement or agitation was also uncommon.

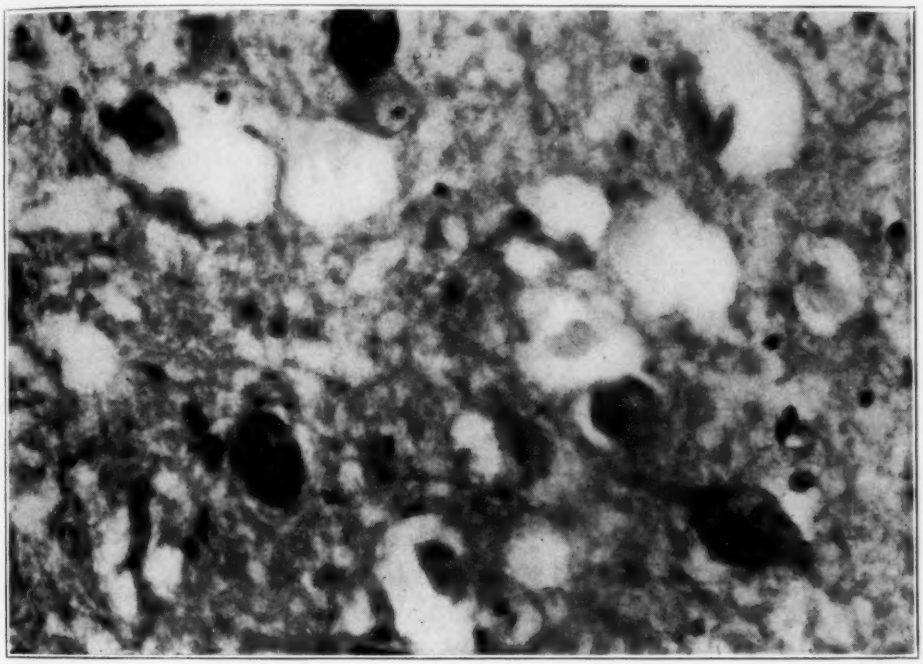

Fig. 4.—Alcoholic psychosis with delirium. High power view of part of nucleus of the third nerve on one side (Masson's trichrome stain), showing liquefaction necrosis in many of the cells.

Table 2 shows the neurologic signs. The most frequent single abnormal sign recorded was the grasping reflex (14 cases). Next was the sucking reflex (13 cases). In 9 cases there were changing rigidities. In 18 of the cases some change in the pupillary reflex, inequality of pupils or paralysis of ocular muscles was presented. In 8 there was nystagmus. In 13 cases there was absence of ankle or knee jerks or both; in many instances this was considered to be evidence of vitamin B_1 deficiency, although tenderness of the calf muscles or hyperesthesia of the soles of the feet was present in only 9 cases. Some evidence of avitaminosis was recorded in 14 cases.

Table 3 shows the general pathologic changes. In all but 1 case there was fatty change in the liver. In only 5 cases was cirrhosis of the liver observed.

In 18 cases disease of the aorta, and in 13 some pathologic condition of the heart, was presented. In 13 cases the kidneys were diseased. In 10 cases there was hemorrhage other than cerebral. The diagnosis of pellagra or scurvy or both was made in 5 cases.

Table 4 shows the pathologic changes in the nervous system. In almost all cases fibrous thickening of the arachnoid was observed. Edema (present in 18 cases) was the next most common change. Petechial hemorrhages were recorded in 16 cases, but in many of these only one small hemorrhage was found after

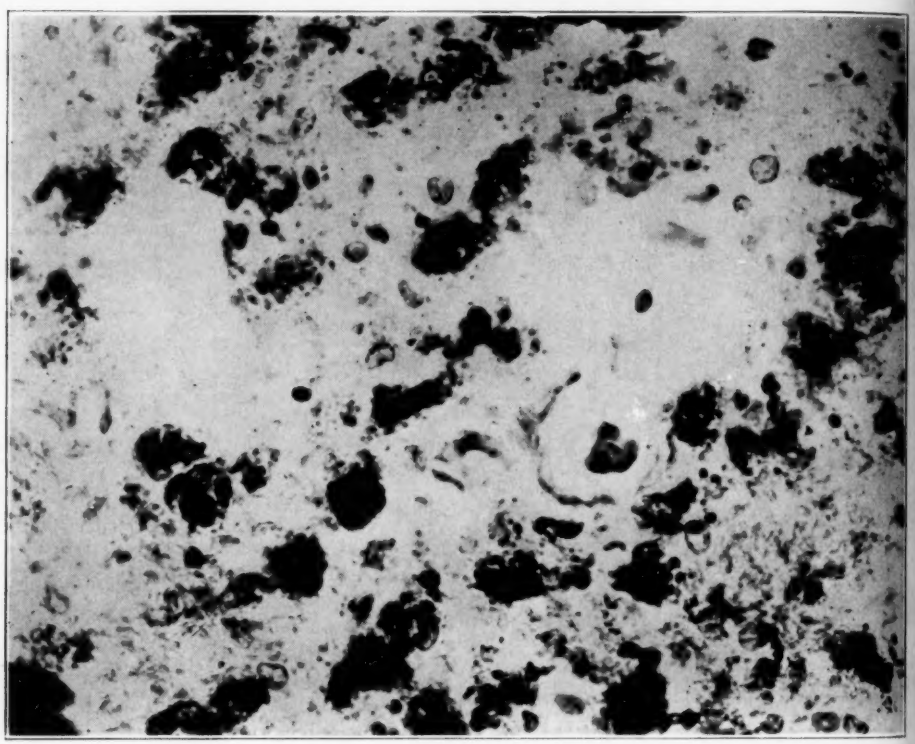

Fig. 5.—Alcoholic encephalopathy. Frozen section through the optic nerve, stained with hematoxylin and sudan III showing a large amount of fat, mostly within phagocytes, in the central portion of the nerve.

careful search. It seems to us that such hemorrhages do not deserve the attention that has been given them in the literature. They were not a prominent feature in our cases. Increase of lipochrome in nerve cells was conspicuous by its absence in the cases of encephalopathy, but was more common in cases of Korsakoff's syndrome. Increase of vascularity was almost absent, except in the mamillary bodies, and there it was found in only 5 cases. Gliosis was present in 8 cases. We spent much time in study of this feature and always used Hortega's stain for neuroglia. We found, in control sections of the floor of the fourth

ventricle and in sections through the walls of the third ventricle, that "gliosis" was normal, and we feel sure that this fact has been overlooked by some authors. Marginal "gliosis" of the cortex of the hemispheres is also a normal observation. Pathologic change in the optic nerves was uncommon. Once or twice we noted some loss of myelin, and in 3 cases fat was present in the central portion

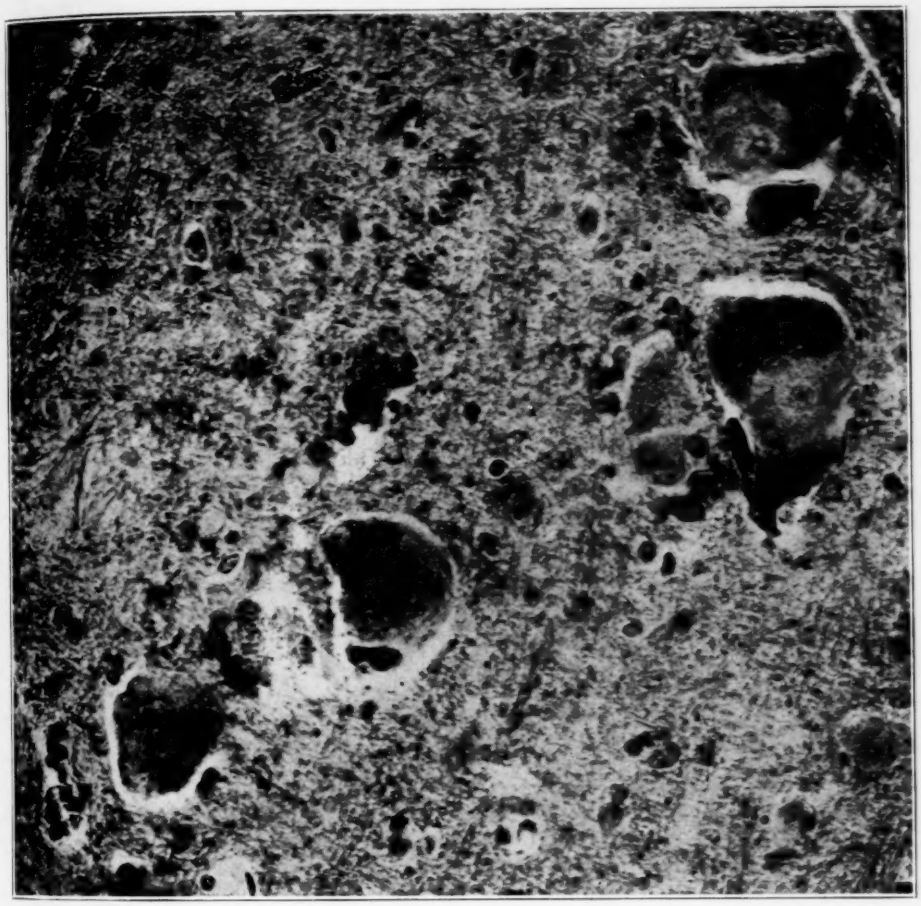

Fig. 6.—Korsakoff's psychosis. Section through the precentral gyrus, stained with hematoxylin and sudan III, showing an increase of lipochrome in and about the nerve cells.

of the nerve, for the most part in gitter cells. Ependymitis was present in 6 cases. This condition also has been misinterpreted by some authors. "Hummocks" in the ependymal lining are found normally in many brains. Changes in nerve cells—chromatolysis, pyknosis and liquefaction necrosis—were recorded in 11 cases. Here, again, caution is needed in calling an occasional pyknotic cell in the cerebellum or elsewhere abnormal.

In at least 50 per cent of the 44 cases of chronic alcoholism the pathologist who removed the brain at autopsy described a notable increase in the amount of fluid in the subarachnoid space. In cases more recently studied this increase of fluid has been noted in practically every case of alcoholism in which autopsy was performed.

Table 5 shows the location of petechial hemorrhages. The wall of the third ventricle and the mamillary bodies were the two chief locations, but, as we have said before, the hemorrhages were insignificant. We believe that few, if any, of these pathologic changes in the brain are due to alcoholism. Some of them are certainly found in deficiency states, especially the increased vascularity of the mamillary bodies, the petechial hemorrhages and the changes in the nerve cells. The morphologic changes are scanty indeed and the pathologic changes responsible for the clinical picture are probably reversible. This theory gains support from

TABLE 5.—*Location of Hemorrhages in Twenty-Two Cases of Alcoholic Encephalopathy* *

Case number...	1	2	3	4	5	N 6	7	8	N 9	10	11	N 12	13	N 14	15	N 16	N 17	N 18	19	20	21	N 22
Subarachnoid..	+	0	+	+	+	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0	0	+
Superior frontal gyrus.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	+	+	0	0	+
Paracentral lobe.....	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	—	—	—	—
Temporal lobe..	+	—	—	—	—	0	—	—	—	—	—	0	—	—	—	—	—	+	—	—	—	—
Hippocampus..	0	+	0	0	0	0	0	—	—	—	0	0	0	0	—	—	0	0	0	—	0	0
Mamillary bodies.....	0	0	+	0	+	0	0	+	0	0	0	0	0	0	+	0	0	+	0	0	0	+
Third ventricle (wall).....	+	0	0	0	0	+	0	0	+	0	0	0	0	0	0	+	+	+	0	+	0	+
Midbrain.....	0	0	0	0	+	0	0	0	0	+	0	0	0	0	0	0	0	+	0	0	0	+
Pons.....	—	—	0	0	0	0	0	—	0	—	0	—	0	0	—	—	—	0	0	0	0	0
Medulla.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0
Cerebellar cortex.....	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dentate nucleus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Corpus callosum.....	0	—	0	0	—	0	0	—	—	0	0	—	—	—	—	—	—	—	—	0	—	—
Cord.....	0	—	—	0	—	—	0	—	—	—	0	—	—	0	—	—	—	—	—	—	—	—
Total areas involved.....	3	1	2	1	3	1	0	2	1	1	1	0	1	0	1	3	1	5	1	1	0	5

* + indicates hemorrhages; 0, no hemorrhages, and —, that no sections were examined.

the therapeutic work of Jolliffe, Bowman, Rosenblum and Fein,[4] in cases in which they made the diagnosis of encephalopathy due to nicotinic acid deficiency. The recent work of Cleckley, Sydenstricker and Geeslin,[23] in cases of atypical psychoses, also supports this view.

SUMMARY AND CONCLUSIONS

The changes in the brain have been studied in 44 cases of chronic alcoholism of various clinical types.

A summary of the clinical and pathologic findings in 22 cases of a condition diagnosed as alcoholic encephalopathy is given in the form of tables. Nine of these cases were regarded as instances of encephalopathy due to nicotinic acid deficiency by Dr. N. Jolliffe.

We have illustrated the most pronounced neuropathologic changes observed in the 44 cases.

The principal conclusions are: (*a*) Since the pathologic alterations in the nervous system in cases of chronic alcoholism demonstrated in this study are relatively slight as compared with the severe and fatal illness of the patient, we believe that the changes usually responsible for death and for the clinical picture cannot be demonstrated under the microscope by methods now at one's disposal. Most of the changes are probably due to avitaminosis (B_1 and B complex) rather than to alcohol itself.

(*b*) There is little correlation between the clinical picture and the anatomic distribution of lesions, except in some cases of Wernicke's syndrome.

(*c*) We are unable to confirm the observations and conclusions of some previous authors with regard to (1) frequent and severe involvement of the optic nerves; (2) frequent and severe lesions in the medulla; (3) frequent changes of importance in the blood vessels; (4) severe ependymitis or gliosis; (5) usual or constant marginal localization of the lesions, and (6) the presence of important lesions in the cerebellum.

STUDIES IN DISEASES OF MUSCLE

IX. EFFECT OF QUININE AND PROSTIGMINE METHYL SULFATE ON MUSCULAR RIGIDITY IN PARALYSIS AGITANS

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Both prostigmine methyl sulfate and quinine are known to influence the effects of stimulation of cholinergic nerves. Prostigmine methyl sulfate increases these effects, and has actions that closely resemble those of physostigmine. It depresses the activity of choline esterase (McGeorge [1]), antagonizes the effects of curare (Briscoe [2]), and has effects on various organs that are similar to those produced by cholinergic nerve stimulation (Aeschlimann and Reinert [3]). On the other hand, quinine reduces the effects of cholinergic nerve stimulation on striated muscle (Harvey [4]) and the salivary glands (Stavraky [5]) and decreases the effects of acetylbetamethylcholine (Starr [6]) and of vagal stimulation on the heart (Lewis, Drury, Iliescu and Wedd [7] and Nathanson [8]).

Recently, both drugs have found a useful place in the management of patients with certain muscular disorders. In myasthenia gravis,

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From the New York Hospital; the Departments of Medicine and Pharmacology, Cornell University Medical College, and the Russell Sage Institute of Pathology.

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muscular weakness and fatigability often are improved promptly, although only temporarily, by the administration of prostigmine methyl sulfate (Walker [9]). In cases of myotonia congenita, quinine often is of value in improving the inability of the muscles to relax promptly after an initial forceful contraction (Wolf [10]). Conversely, quinine increases the muscular symptoms in myasthenia gravis, and prostigmine accentuates those in myotonia congenita. On the basis of these facts, some writers have postulated that the effects of the two drugs are specific in myasthenia gravis and myotonia congenita, and that they indicate the nature and site of the defect in these conditions (Kennedy and Wolf [11] and Harvey [12]). However, the observation by Hassin [13] that quinine reduces muscular stiffness in dystonia musculorum deformans and my studies [14] on the effect of prostigmine methyl sulfate in cases of myasthenia gravis raise considerable doubt regarding the validity of this assumption.

In the investigations reported here, the effects of quinine and prostigmine methyl sulfate on muscular rigidity in 8 patients with paralysis agitans were studied. The amount of muscular rigidity differed widely in these patients. Two of the patients had only slight stiffness of a few muscle groups; 4 had moderate rigidity of two or more extremities, and in 2 subjects the stiffness was considerable and involved most of the voluntary muscles of the body.

METHODS AND RESULTS OF INVESTIGATION

Quinine.—Quinine was administered for periods of from two weeks to several months, and there were several alternate periods of control and of quinine administration. The dose in most instances was 0.3 Gm. of quinine sulfate, taken orally, two or three times a day. Larger amounts, when given over periods of several days, usually produced side effects, such as buzzing in the ears and dizziness. Six of the patients were receiving scopolamine daily at the time these studies were started.

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The use of scopolamine was continued unchanged throughout all periods of investigation, except occasionally when the effect of interrupting its administration was studied. In 1 experiment (case 8) quinine was administered intravenously.

In brief, the results were as follows: (*a*) In 2 patients muscular rigidity was much decreased. In 1 of these patients the stiffness had been considerable and in the other moderate. The muscular pain, of which both patients had complained, and the rigidity of the jaw muscles in 1 patient, which had resulted in continual drooling of saliva and in malnutrition, were relieved considerably. Quinine had greater effect on muscular pain than had equivalent doses of acetylsalicylic acid. The effect of quinine on the tremor was slight in 1 patient and was not demonstrable in the other. (*b*) In 2 patients moderate reduction in muscular stiffness was observed. One patient had an advanced stage of the disease; muscular rigidity was considerable and involved most of the voluntary muscles of the body. The patient was unable to walk or to get up from a chair without assistance, and constant drooling of saliva and a violent tremor constituted distressing symptoms. In the second patient, both the muscular rigidity and the tremor were of moderate severity. Both patients complained of muscular pains, which were much decreased after taking quinine. The tremor was decreased slightly in the patient with the advanced stage of the disease and was unaffected in the other. (*c*) In 4 patients the effect on symptoms was absent or only slight. Two of these patients had only slight muscular rigidity; in the other 2 the muscular stiffness was moderate. The tremor in all instances was slight. Three of the patients were able to take only 0.2 or 0.3 Gm. of quinine sulfate twice a day because larger doses induced undesirable side effects.

Decreasing Effect of Quinine After Prolonged Administration: Patients in whom quinine had a definite effect on muscular rigidity continued to derive benefit from the medication for periods of about one to four months. Toward the end of this period, quinine when taken in constant doses daily had a decreasing effect on muscular stiffness. In some instances this effect diminished until it was practically absent. After the administration of the drug had been interrupted for a few weeks, the effect on muscular stiffness again became evident. However, this effect appeared to be greater during the first period than during a subsequent period of administration of the drug.

Prostigmine Methyl Sulfate.—The effect of prostigmine methyl sulfate on muscular rigidity was studied in a series of observations on 4 patients. The usual dose of the drug was 1.5 mg., given subcutaneously. In all experiments on the same patient the degrees of depression induced by prostigmine methyl sulfate in the activity of serum choline

esterase were similar. In several instances the influence of scopolamine, atropine and quinine on the muscular effects of prostigmine methyl sulfate was studied also. Briefly, the observations were as follows: The administration of prostigmine methyl sulfate was followed, within fifteen minutes, by considerable increase in both the rigidity and the tremor of the muscles. In 1 patient (case 2), with symptoms of only moderate severity, the clinical picture rapidly developed into one resembling a far advanced stage of the disease. Muscular rigidity of cogwheel character became severe in all extremities, and tremor, which had previously been moderate, became violent. The patient experienced diplopia, although he had never had this complaint before. In another patient (case 4) cogwheel rigidity developed in an extremity in which previously no muscular rigidity could be demonstrated.

The administration of atropine rapidly abolished the effects of prostigmine methyl sulfate in all patients, and within ten minutes the

Effects of Quinine, Prostigmine Methylsulfate and Scopolamine on Paralysis Agitans (Case 2)

Drug	Effect on Muscular Rigidity and Tremor
Scopolamine alone	Decrease ++
Quinine alone	Decrease +
Scopolamine and quinine	Decrease +++
Prostigmine methyl sulfate alone	Increase ++++
Prostigmine methyl sulfate after scopolamine	Increase + or 0
Prostigmine methyl sulfate after quinine	Increase ++ or +++

symptoms returned to their previous status. Scopolamine, given within a few hours before the administration of prostigmine methyl sulfate, reduced or prevented the effects of the latter on muscular rigidity and tremor. Similarly, when quinine was taken previously prostigmine methyl sulfate had less muscular effect. However, for the doses given this influence of quinine on the effects of the prostigmine salt was less than that of scopolamine. The results observed in the experiments on 1 patient (case 2) are summarized in the table.

The administration of similar amounts of prostigmine methyl sulfate to normal subjects or to patients with progressive muscular dystrophy was not followed by development of muscular stiffness. However, in patients with myotonia congenita and myotonia atrophica an increase in the inability of the muscles to relax after an initial forceful contraction was observed when prostigmine methyl sulfate was given.

The effect of prostigmine methyl sulfate on muscular rigidity in cases of paralysis agitans is not related to any unusual activity of the choline esterase in this condition. Since the subject of serum esterase activity was discussed in a previous report (Milhorat [15]), no data are given here.

15. Milhorat, A. T.: The Choline-Esterase Activity of the Blood Serum in Disease, J. Clin. Investigation **17**:649, 1938.

COMMENTS AND SUMMARY

Quinine reduced muscular rigidity in several patients with paralysis agitans. Concomitant with the diminution in muscular stiffness there often was reduction in muscular pain. The effect of quinine on muscular pain was greater than one would expect from the analgesic action of the drug and appeared to depend largely on the reduction of muscular stiffness.

After quinine had been taken daily for several weeks the muscular effects gradually diminished. However, when the drug was stopped for a few weeks renewed administration usually was followed again by apparent effects on muscular rigidity. The results indicate that in certain patients with paralysis agitans quinine is of value in temporarily reducing muscular stiffness.

Prostigmine methyl sulfate increased muscular stiffness and tremor in paralysis agitans. One patient who never had had diplopia before experienced this disability when the drug was given. In another patient, prostigmine methyl sulfate induced rigidity and tremor of an extremity that had been free from all signs of paralysis agitans. When similar doses of prostigmine methyl sulfate were administered to normal subjects no rigidity or tremor was observed. It is probable that in paralysis agitans larger amounts of acetylcholine are produced in the muscles than normally because of the increased nerve stimulation. An increased production of acetylcholine in the muscles could account for the observed effects of prostigmine methyl sulfate.

Atropine and scopolamine abolished and prevented the effects of prostigmine methyl sulfate on the muscles. It is of interest that a similar antagonistic action is not observed in cases of myasthenia gravis. This effect of atropine and scopolamine most likely is due to peripheral action of the drugs, although the main action of scopolamine, which makes the drug of value in the management of paralysis agitans, appears to be a central one.

The previous administration of quinine did not prevent, but definitely reduced, the muscular effects of prostigmine methyl sulfate.

Quinine and prostigmine methyl sulfate were observed to have effects in some patients with paralysis agitans that were similar to those seen in patients with "myotonia." Hence the assumption that the effects of these drugs indicate the nature of the defect in "myotonia" appears unjustified. It is probable that the effect of quinine on muscular function in cases of "myotonia" and paralysis agitans is the result of the antagonistic action of the drug to cholinergic nerve stimulation.

REPORT OF CASES

CASE 1.—A Jewish housewife aged 51 years was first seen in the New York Hospital on Oct. 29, 1934. Four years before her admission her family noticed the gradual development of a fixed staring expression. Shortly after, she began

to complain of difficulty in swallowing and drooling of saliva. All these complaints progressed slowly up to the time of her admission. The past history was noncontributory except that nine years before the onset of her symptoms the patient had had a persistent headache for six months.

Examination.—In 1934 it was observed that the patient walked slowly in a slightly stooped attitude. The facial expression was fixed; the eyes stared and blinked only occasionally. The mouth was held slightly opened and was filled with saliva. The pupils were regular and reacted sluggishly both to light and in accommodation. There was slight tremor of both hands only on initiation of voluntary movements. No rigidity of the extremities could be demonstrated.

Course.—The patient was given 0.6 mg. of atropine sulfate three times a day, without effect on the symptoms. Some improvement in the excessive salivation followed when 0.6 mg. of scopolamine hydrobromide, three times a day, was substituted for the atropine. However, she still had difficulty in swallowing coarse foods. The patient was continued on this regimen until May 1935, when 30 drops of tincture of stramonium, three times a day, was substituted for scopolamine. There appeared to be slight improvement in symptoms after this change in medication. However, in January 1937 the patient complained of increasing tremor and stiffness of the left arm. Two months later the stiffness of the muscles of the jaw increased, making it difficult for her to eat. She stated that she often had blurring of vision and found it necessary to decrease the amount of tincture of stramonium to 20 drops three times a day. The stramonium was discontinued and 0.4 mg. of scopolamine hydrobromide was given four times a day, without much change in the symptoms. The status of the patient's condition in August 1937 was as follows: The facies was masklike. The eyes stared, blinking only occasionally. There were superficial excoriations of both corners of the mouth, where saliva drooled constantly. The patient walked slowly and with a slight stoop. The arms were held rather rigidly in a semiflexed position close to the body. There was considerable coarse tremor of the left hand and forearm, which disappeared on purposive movement. All movements were performed slowly. There was definite increase in resistance to passive stretching in both arms; the stiffness was more pronounced on the left side. The increase in resistance to passive stretch in the lower extremities was moderate.

Under a regimen of 0.6 mg. of scopolamine hydrobromide three times a day the patient's symptoms continued unchanged. Any increase in the dose of scopolamine was followed by blurring vision. On April 20, 1938 the patient was given 0.3 Gm. of quinine sulfate three times a day in addition to the scopolamine. Within a day after starting this medication the rigidity of the muscles of the jaw was much decreased, so that the difficulty in opening and closing the jaw in eating had practically disappeared. Drooling of saliva was relieved almost completely. The rigidity of the muscles of the extremities was much improved, but the tremor appeared not to be affected. For the first time in over two years the patient was able to perform some household duties.

The symptoms continued in this improved state for about five months, except on a few occasions when the patient failed to take quinine for a day or two. On each occasion on which quinine was not taken muscular rigidity increased and drooling of saliva returned. In October 1938 the effect of quinine on muscular disability gradually diminished until, a few weeks later, little beneficial effect was apparent. Quinine was discontinued at this time, with little or no change in symptoms. No quinine was taken for the next month. In December 1938 the patient complained of muscular pains. At this time both muscular rigidity and drooling of saliva were considerable. The administration of 0.3 Gm. of quinine

sulfate twice a day was followed by a decrease in these symptoms. The effect of quinine on the symptoms was evident for about four weeks. At the end of this period the beneficial effect of the drug gradually diminished. In the following year (from December 1938 to December 1939) quinine was given for several periods, each three to six weeks in length. In every instance the effect of quinine during the early part of the period was to decrease muscular rigidity, provided no quinine had been taken for at least two to three weeks previously. Furthermore, in every instance the effect of quinine on muscular stiffness diminished after the drug had been taken daily for four weeks or more.

CASE 2.—A Jewish house painter aged 49 entered the New York Hospital on June 24, 1935, complaining of tremor of the right hand. Eight months before his admission the patient had noticed tremor of the hand, which gradually increased. The tremor in the course of about six months had increased to the point at which the patient had to give up work. About two and a half years previously a friend had noticed that when the patient walked the right arm was held motionless, but the patient otherwise had been unaware of this. The patient had had no illness suggestive of "encephalitis" or "influenza" during the ten years preceding his admission.

Examination.—The facies was moderately fixed and expressionless. The pupils were equal and reacted well both to light and in accommodation. The extraocular movements were normal. The muscles of the right arm showed slight increase in resistance to passive stretch, and rapid rhythmic alternating movements of the right hand were awkward. There was moderate tremor of the right hand. The patient walked with the right arm held stiffly to the side; the left arm swung freely.

The patient was given 0.3 mg. of scopolamine hydrobromide three times a day, with moderate improvement in his symptoms, and was discharged to be followed by his private physician.

Second Admission.—On Jan. 17, 1938 the patient was readmitted to the hospital. Six months previously he had begun to complain of pain in the left leg. The pain was felt in the peroneal muscles and was worse at night, often interfering with sleep. Examination showed that all symptoms had increased considerably since the patient had last visited the clinic. He walked slowly and stiffly, with both arms held in a partly flexed position. The facies was masklike; the eyes stared, and winked only infrequently. The pupils were equal and reacted to light but not in accommodation. The tongue showed a definite tremor when it was protruded.

Course.—The patient was continued on the regimen of 0.3 mg. of scopolamine hydrobromide three times a day. The symptoms continued unchanged. On April 27, 1938 0.3 Gm. of quinine sulfate, three times a day, was given. Administration of scopolamine was continued unchanged. The muscular rigidity was decreased to the extent that it disappeared almost entirely within a few days after the qninine was begun. The pain in the leg subsided and did not recur. Since these amounts of quinine induced slight dizziness the dose was decreased to 0.3 Gm. twice a day. The improvement in muscular rigidity and pain continued on this regimen. The patient was now able to perform activities he had been unable to carry out previous to the administration of quinine. After about five weeks the beneficial effect of quinine gradually decreased. The feeling of tiredness, of which the patient had complained previously and which had been relieved after taking quinine, returned. On interrupting the administration of quinine, muscular rigidity and tremor increased and pain in the leg recurred. Administration of quinine was followed again by decrease in all symptoms, but the drug appeared to be not as effective as when it first was tried. The patient continued to take quinine for

the next nine months (up to March 1939), with occasional interruptions in order to observe the effect. On each occasion on which quinine was stopped muscular stiffness increased and pain returned. Acetylsalicylic acid relieved the pain about as well as the quinine, but had to be taken in amounts of 0.6 Gm.

In May 1939 it appeared that quinine no longer was having much effect on the muscular symptoms. When quinine was stopped at this time no change in symptoms could be demonstrated. No quinine was taken for the next two months. In July 1939 the effect of 1.5 mg. of prostigmine methyl sulfate, given subcutaneously, was studied. The effect of prostigmine was to increase the muscular rigidity and tremor in a striking manner. Before the drug was given muscular rigidity and tremor were moderate. The patient was able to walk fast, but the left arm hung limply and the right arm was held flexed. Both arms showed only a moderate amount of associated movements. The choline esterase activity of the serum was 1.24. Within fifteen minutes after prostigmine methyl sulfate was administered the clinical picture was changed from one of paralysis agitans of moderate severity to one almost of the extreme stage of the disease. There was marked cogwheel rigidity of all the extremities. The jaw moved in constant violent tremor. The tremor of the extremities was so severe that the patient had difficulty in sitting on a chair. The gait was slow and shuffling, with a tendency to trip; the entire body was held rigid and bent far forward. The facies was fixed, and the patient complained of diplopia. The choline esterase activity of the serum was 0.94. Within four minutes after the subcutaneous administration of 0.6 mg. of atropine sulfate rigidity and tremor were much improved. A similar dose of atropine was repeated at this time, and within three minutes the muscular effects of the prostigmine were abolished completely. The diplopia disappeared and muscular rigidity and tremor diminished until they were the same as before the administration of prostigmine.

On the following day the observations were repeated. However, the patient had taken three doses of 0.3 Gm. of quinine sulfate within the twelve hours preceding the administration of prostigmine. The choline esterase activity of the serum was 1.25. The effect of quinine was to diminish the muscular effects of prostigmine. Prostigmine methylsulfate increased all symptoms of paralysis agitans, but not nearly as much as on the previous day, when no quinine had been taken. Diplopia did not develop. The depression in esterase activity of the serum was similar to that on the previous day, the level being 0.88. After the subcutaneous injection of 0.6 mg. of atropine sulfate the condition of the patient reverted in a few minutes to its previous status.

The patient was placed on a regimen of 0.3 mg. of scopolamine hydrobromide three times a day. During occasional periods of from four to six weeks quinine was given in addition to the scopolamine. During these periods further diminution in muscular stiffness was observed.

CASE 3.—An unmarried woman aged 23 entered the New York Hospital on Dec. 8, 1936, complaining of tremor and weakness of the right extremities, difficulty in enunciating words and slight drooling of saliva. Five years before her admission she had noticed some difficulty in talking; the voice was hoarse, and the letter "s" was not pronounced as distinctly as before. This disability continued practicaliy unchanged up to the date of admission. Two years before her admission there had developed tremor of the right leg, and shortly afterward the right arm became involved. Both extremities appeared to be weaker than before, and occasionally the patient noticed a limp of the right leg. Both tremor and weakness increased

slowly during the following two years. About one year before her admission the patient noticed that saliva accumulated in the mouth, a complaint that remained almost unchanged up to the time she was seen in the clinic. There was no history of preceding illness suggestive of encephalitis. A brother, aged 21, gave a history of becoming nauseated whenever he took 0.3 Gm. or more of quinine.

Examination.—When the patient walked the right arm was held close to the side in an extended position, whereas the left arm moved freely. The pupils were equal and regular and reacted to light and in attempts at near vision. The extraocular movements were normal. The face was expressionless. Speech was of monotonous quality. There was slightly increased resistance of the muscles of the right arm and right leg to passive stretch. Both right extremities showed a moderate tremor. Alternating rhythmic movements were made slowly and somewhat awkwardly by the right hand. The right hand felt colder than the left to both the patient and the examiner.

Course.—The patient was given scopolamine hydrobromide, 0.3 mg. ($\frac{1}{200}$ grain) three times a day, with considerable improvement in all the symptoms. Tremor, muscular weakness and salivation were decreased. In June 1938 she was given 0.3 Gm. (5 grains) of quinine sulfate twice a day in addition to scopolamine. No further improvement in muscular symptoms was observed. Larger amounts of quinine were not given because of side effects, such as nausea and dizziness.

The patient was continued on a regimen of scopolamine hydrobromide, 0.3 mg. three times a day. Up to Feb. 20, 1940 the symptoms had remained unchanged.

Case 4.—An American-born student aged 20 entered the New York Hospital on Jan. 27, 1939, complaining of weakness of the left arm and leg, and a limp of the left leg of five months' duration. In September 1938 the patient had first noticed a limp in the left leg, with slight increase in fatigability. The condition remained unchanged until about four months later, when stiffness of the affected extremity developed. About one month later he noticed that the left hand was held close to the side of the body when he walked and that the arm did not swing as freely as before. At that time the patient began to complain of tremor of the left hand and of increasing fatigability of both left extremities. He entered a nearby hospital, where roentgenographic studies of the spine were made and lumbar puncture was performed. No diagnosis was made. The past, personal and family histories were noncontributory. There was no history suggestive of encephalitis.

Examination.—There was disclosed the disability of which the patient complained. In addition, the following significant findings were demonstrated: In walking the left leg was not flexed in a normal manner, but was held partially extended and associated movements of both left extremities were practically absent; there was moderate lordosis; the left arm was kept in a partially flexed attitude; there was moderate tremor of the left hand and left foot; rapid alternating rhythmic movements were performed poorly with the left arm and leg; both left extremities showed a cogwheel type of movement and increased resistance to passive stretch.

Course.—In March 1939 the effect of 0.3 mg. of scopolamine hydrobromide given three times a day was studied. There was moderate decrease in muscular stiffness and tremor during the period in which the drug was administered.

On May 3, 1939 the patient was placed on a regimen of 0.3 Gm. of quinine sulfate three times a day. There were slight relief of the ache in the left leg

and only slight diminution in the muscular stiffness. The patient complained of moderate sensation of buzzing in both ears.

On May 20, 1939 the patient entered the hospital for the purpose of determining the effect of sulfanilamide on the course of the disease. No therapeutic effect of sulfanilamide could be demonstrated.

On July 5, 1939 1.5 mg. of prostigmine methylsulfate (3 cc. of a 1:2,000 solution) was administered subcutaneously. The effect was to increase rigidity and tremor of the left extremities. In the right arm, which before the injection of the prostigmine had never shown stiffness or tremor, definite rigidity of cogwheel type developed. The effect of the prostigmine was abolished within twelve minutes after 0.6 mg. of atropine sulfate had been given subcutaneously.

No further medication was given until September 1939, when 0.3 Gm. of acetylsalicylic acid three times a day was prescribed. The effect of acetylsalicylic acid on the muscular pain was about the same as that of equivalent doses of quinine sulfate.

On Nov. 7, 1939 the administration of 0.3 Gm. of quinine sulfate three times a day was started and continued for three weeks. No definite effect except moderate diminution in pain was observed. Scopolamine hydrobromide, 0.3 mg. three times a day, was started on Dec. 5, 1939. There was moderate improvement in muscular rigidity and tremor, but no appreciable effect on the pain in the left leg.

CASE 5.—An American-born salesman aged 51 entered the New York Hospital on Nov. 15, 1938. For two years preceding his admission to the hospital the patient had noted weakness and stiffness of the right arm. When he extended the arm there was tremor of the fingers. He stated that when the arm was flexed and held against the body the tremor was absent. The disability of which the patient complained had been very slowly progressive up to the time he first was seen in the hospital. The past, personal and family histories were noncontributory.

Examination.—The patient walked with a slight stoop and with the right arm held close to the body in a flexed position. There was slight diminution in the facial movements. Otherwise the significant findings were limited to the right upper extremity, in which there were slightly increased resistance to passive stretch, with movements of cogwheel character, and slight tremor. The muscles of the upper right arm showed moderate diminution in power. Rapid alternating movements were performed awkwardly by the right hand.

Course.—Administration of quinine was started on Jan. 11, 1939, but because of a buzzing sensation in the ears the patient was able to take only 0.3 Gm. of quinine sulfate two times a day. The muscular stiffness, which had been slight, practically disappeared. However, the tremor and the symptom characterized by the patient as "lameness" were unaffected.

On Jan. 25, 1939 the patient was placed on a regimen of 0.3 mg. of scopolamine hydrobromide three times a way, with definite improvement in all the symptoms. The administration of scopolamine was continued except for an occasional period. During the periods in which no scopolamine was taken tremor and muscular rigidity were increased.

In October 1939 pain developed in the region of the right shoulder, with findings suggestive of subdeltoid bursitis. After several weeks of physical therapy the pain in the shoulder gradually improved. At about the same time the tremor

increased slowly. Although scopolamine was effective in decreasing this symptom, the tremor was more marked during this period of administration than it had been previously.

CASE 6.—A Czechoslovakian housewife aged 54 entered the New York Hospital on July 12, 1938, complaining of tremor of the arms and legs of two years' duration. The onset of the symptom was gradual. The tremor had increased slowly but steadily in intensity up to the time of her admission to the hospital.

The past history revealed that seven years before her admission the patient had fallen down a flight of stairs and injured her back. Because of pain in the lower part of the back, which had persisted since the accident, the patient stooped far over while walking.

Examination.—The patient walked with a very marked stoop. The face was expressionless and the voice of monotonous quality. There was definite tremor of the left leg and left hand, which disappeared when the extremities were in motion. There was moderate rigidity of cogwheel character in both left extremities. Examination showed evidence of generalized arteriosclerosis. The blood pressure was 154 systolic and 100 diastolic.

Course.—The patient was placed on a regimen of 0.4 mg. (1/150 grain) of scopolamine hydrobromide three times a day, with the result that the tremor was slightly diminished and muscular rigidity was moderately reduced. On May 31, 1939 quinine sulfate, in amounts of 0.2 Gm. twice a day, was prescribed in addition to the scopolamine, the administration of which was continued unchanged. The effect of quinine was further moderate improvement in muscular stiffness. This effect was apparent for about four months. At the end of this period the influence on muscular rigidity became progressively less, so that when the administration of quinine was discontinued on Oct. 31, 1939 practically no change in the muscular stiffness could be observed.

CASE 7.—An American housewife aged 38 entered the New York Hospital on Sept. 15, 1937, complaining of tremor. Two years previously the patient had first noticed tremor of the tongue and a few months later tremor of the left hand. The tremor slowly but steadily increased in severity, and three months before admission she began to complain of tremor of the left foot. About a year after the onset of her symptoms she began to have occasional attacks during which the eyes would turn involuntarily to one side or the other. The past history was important in the that patient had a severe attack of encephalitis in 1922.

Examination.—The patient walked with short, halting steps and with both arms held in a flexed position close to the trunk. There was a fixed expression of the face, and the mouth was held partly open. All movements were slow. The tongue and both left extremities showed a coarse tremor. The left arm and leg showed considerable stiffness of a cogwheel character; in the right arm resistance to passive stretch was moderate.

Course.—The patient was given 0.4 mg. (1/150 grain) of scopolamine hydrobromide three times a day. On this regimen there was moderate improvement in muscular rigidity for about three months, but the symptoms continued to progress slowly.

On June 29, 1938 the patient was given quinine sulfate, which was taken in amounts of 0.3 Gm. twice a day, in addition to the scopolamine, which was continued unchanged. The patient complained of buzzing in the ears when this amount of

quinine was taken, and therefore the dose was reduced to 0.3 Gm. twice a day. On this regimen slight diminution in muscular rigidity and tremor occurred.

CASE 8.—A telephone operator aged 22, unmarried, entered the New York Hospital on June 26, 1933. Three years previously she had begun to have weakness of the right leg, with tremor of the right leg and right hand, which increased steadily.

During the year preceding her admission she noticed occasional tremor of the left side of the lips and gradual loss of the normal movements of the face. Her family stated that the patient showed a tendency to become more irritable than before the onset of her illness. The past history disclosed that she had had influenza in 1918.

Examination.—In 1933 it was observed that when the patient walked her back was arched backward, with considerable lordosis; the left leg was held stiffly, and the left foot was in equinus position. The right arm was held in a flexed position close to the body. Both right extremities showed definite tremor and considerable diminution in power. The movements of all extremities were slow. Increased resistance of a cogwheel type to passive stretch was considerable in the right extremities and slight in the left.

Clinical Course up to Time of Studies on Quinine.—The symptoms progressed steadily, with definite increase in muscular rigidity and tremor. Scopolamine given in doses found to have maximal effects was of only moderate benefit. In May 1938, when the effects of quinine were studied, the condition of the patient represented a far advanced stage of paralysis agitans. The face had a masklike appearance and the mouth was held half opened, showing the tongue in constant tremor. The trunk and extremities were held partially flexed, and the patient was unable to get up from a chair without assistance, and even then with difficulty. Walking could be accomplished only with assistance and consisted of short shuffles of one foot after the other. The right arm showed considerable rigidity of a cogwheel type on passive stretch. The left arm and both lower extremities were stiff, but rigidity was not as pronounced as in the right arm. The patient complained of moderate pain in the muscles of both upper extremities.

Effects of Quinine.—The patient was given 0.25 Gm. of quinine hydrochloride by slow intravenous injection. Within ten minutes the right arm was less rigid and the face less masklike. The difficulty in walking appeared not to be improved.

The patient was placed on a regimen of 0.3 Gm. of quinine sulfate three times a day in addition to the scopolamine which she had been taking. The effect of the quinine was moderate reduction in stiffness of both arms, so that the patient was able to feed herself. Moreover, the pain in both arms of which she had complained was relieved. After about four weeks the effect of quinine became less evident; muscular pain returned, and muscular stiffness appeared to be progressively less affected. Because of the advanced state of the disability the patient was admitted to a hospital for chronically ill patients.

SEEPING INTRACRANIAL ANEURYSM SIMULATING NEOPLASM

SYNDROME OF THE CORPUS CALLOSUM

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Two cases will be reported and 6 others from the literature noted in which an intracranial aneurysm gave rise to chronic increase in intracranial pressure. The features serving to differentiate cases of this lesion from those of neoplasm will be indicated. In the first case the lesion in the corpus callosum was one of the most sharply circumscribed on record, and the localizing signs thereof will be discussed.

REPORT OF CASES

CASE 1.—*History.*—A woman aged 57, the wife of a college president, entered the Billings Hospital on Oct. 2, 1938, having been referred to Dr. Percival Bailey by Dr. A. Richard Kent, of Springfield, Ohio. The symptoms of her illness had begun suddenly seven weeks previously. While glancing in a mirror she felt an indescribable feeling of terror come over her, noted that her pupils were dilated and threw herself on the bed. She became unconscious and remained so for an hour and a quarter. There were no tonic or clonic movements. When she recovered consciousness she was very weak, her speech and writing were slightly less clear than normal, she vomited a great deal and she complained constantly of pain in her head. There was pronounced urgency of micturition. Dr. Kent saw her two days later and noted that her optic fundi were normal. There was gradual recovery, nearly complete, from all of the aforementioned symptoms and signs during a period of four weeks, but at the end of that time inaccurate memory for recent events and occasional difficulty in recalling the names of common objects appeared. For the entire period the patient observed that she was unable to release voluntarily anything she had grasped with the right hand. Her nurse had to pry objects out of that hand, and when the patient clasped the fingers of the two hands together she was unable to separate them.

Five weeks after the first ictus she became angry with her maid one morning, suddenly saw great flashes of light before her eyes, had a severe headache, became bewildered and began to vomit. Lumbar puncture several days later revealed an initial pressure of 215 mm. of cerebrospinal fluid, and there were 2 white blood cells per cubic millimeter of fluid. One week after this the fundi were abnormal for the first time, showing bilateral papilledema with retinal hemorrhages. A few days later she was walking back to her bed from the bathroom when she felt as though she were being drawn backward, took a few short steps backward and then

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fell, striking the occiput smartly on the floor. She was not unconscious. She had had three other falls during this period, owing to her unsteadiness.

In her past history the following is pertinent: When she was 45 years of age she was found to have hypertension, and the systolic blood pressure had since fluctuated between normal levels and 200 mm. of mercury. Two of her siblings and her father had died of cerebral hemorrhage and her mother of "angina." She had always been energetic and highly intelligent. The latest indication of this was just before her present illness, when the family had moved to a new house. She measured all of the furniture and arranged it on an accurate floor plan of the new residence, so that when moving occurred each piece was taken directly to its appointed place. She had always been markedly right handed, and carried out all forms of unilateral activity involving the upper limbs with the right by preference.

Examination.—On admission (October 2) only the following abnormal findings were revealed: (1) bilateral papilledema, 2 D. in the right eye and 1.5 D. in the left, many large retinal and subhyaloid hemorrhages about each optic disk and generalized narrowing of the retinal arteries and engorgement of the veins; (2) minimal dysarthria; (3) inconstant forced grasping in the right hand—when the flexor tendons of the fingers were stretched she was often unable to relax them voluntarily; (4) extremely unsteady gait—she could take only a few mincing steps unassisted, and (5) impaired capacity to concentrate and slight inconsistencies in her version of her clinical history. The blood pressure varied from 110 to 136 mm. of mercury systolic and from 76 to 88 mm. of mercury diastolic.

With the right hand the patient wrote well, both spontaneously and to dictation; she copied print and cursive script, and transcribed from one to the other, and she copied a drawing of a birdhouse. She solved difficult problems in mental arithmetic promptly, but hesitated in giving the names of two of twenty common objects. She used promptly in a sentence three nouns given her at random, and performed promptly Marie's three paper test. Shown a complex picture, she named the six colors and the various objects in it and grasped its general significance promptly. She read a newspaper aloud well, and understood and repeated moderately well the contents of one of its paragraphs. Given the anagrams B G R I O Y L and told to select the letters of a word indicating "male child" and "female child," she was unable to pick out either "boy" or "girl," but promptly formed these words on direct request. She obeyed commands requiring complicated movements with each hand. The foregoing tests are described in detail to show that the patient had only a minimal degree of semantic and amnesic aphasia.

Roentgenograms of the skull and the chest were normal. Electroencephalograms showed wavelike forms of irregular frequency occurring in short runs and arising about equally from the two frontal lobes; Dr. T. J. Case, however, expressed the opinion that these furnished insufficient evidence for a diagnosis. Ophthalmologic examination revealed concentrically constricted visual fields and enlarged blindspots. Visual acuity was at the lower limits of normal in each eye. Audiometric examination demonstrated minimal loss of acuity in the high tone ranges bilaterally. The caloric reactions were normal, and there was no positional nystagmus.

On five examinations the urine showed a minimal trace of albumin; the values for urea clearance were nearly normal on two tests. All other examinations of the blood and urine, including Wassermann and Kahn tests of the blood, gave normal results. Dr. Louis Leiter, the medical consultant, expressed the opinion that the mental and retinal changes were not due to renal or hypertensive disease.

Ventriculography.—This was performed by Dr. Bailey, with a preoperative diagnosis of unlocalized tumor of the brain. At the operation, air injected into one posterior horn bubbled freely out of the other side, together with clear, colorless ventricular fluid. The ventriculogram showed moderate generalized dilatation of both lateral ventricles and of the third ventricle (fig. 1). No air had entered the fourth ventricle.

Reexamination.—Dr. Bailey then asked Dr. Peter Bassoe to examine the patient with him; during this complete neurologic examination the previous findings were confirmed, and severe ideomotor apraxia was found to have developed on the left side. When ordered, "Put your right little finger on your left ear," the patient did so promptly. But the command, "Put your left index finger on the tip of

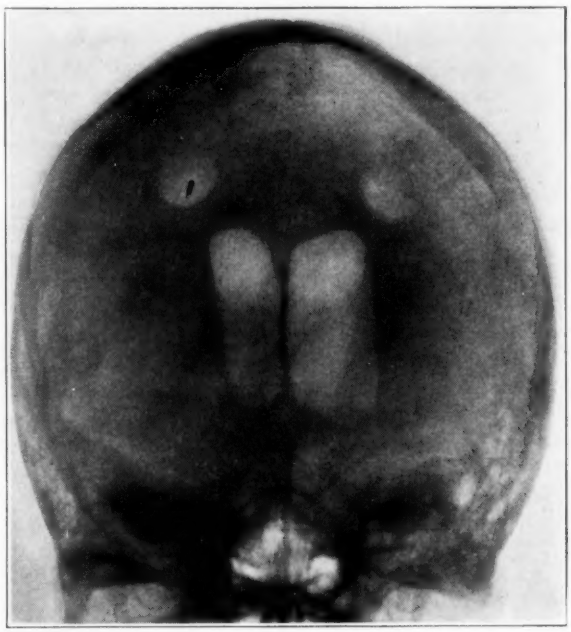

Fig. 1.—Ventriculogram. The dilated lateral and third ventricles are shown.

your nose," resulted at first in no response. She said she was "trying to make the hand go up there but it just would not go." Asked to indicate her left index finger, she extended it; asked to point to her nose, she promptly did so with the right hand and then said: "Now you want me to put my left index finger on my nose." She then put that finger into her mouth and said: "That's funny; why won't it go up to my nose?" The movement of the left hand to the mouth was well coordinated and without tremor. Shortly, the patient casually scratched her head with her left hand. Her ability to execute all commands with her right hand plus her accurate verbal paraphrasing of the command clearly showed that she understood perfectly. During the next three days this finding was repeatedly confirmed. The left lower limb, the right limbs and the face never showed any apraxia, but with the left upper limb a wide variety of commands were executed either with gross inaccuracy or not at all. With her eyes closed the performance

of the left arm was slightly but inconsistently improved. She was unable to imitate with the left hand the examiner's movements. Execution of actions in pantomime was normal with the right hand, but the left was simply "flopped about." When such actions involved the use of both hands, the right performed in essentially normal fashion but the left did not; the left hand was not helped and the right was not hindered significantly by the bimanual nature of the task. Writing with the right hand was normal; that with the left hand was an unformed scribble, not only when done spontaneously but also when done to dictation and in copying. The fingers held the pencil normally, but the forearm, hand and fingers were not moved properly.

Strength, tonus and coordination of all limbs were normal, and sensation, including localization, stereognosis, two point discrimination, proprioception, vibration, touch and pain were all nearly normal, although the patient's capacity for concentration was sufficiently impaired to make critical sensory testing difficult throughout the period before and after the ventriculographic study.

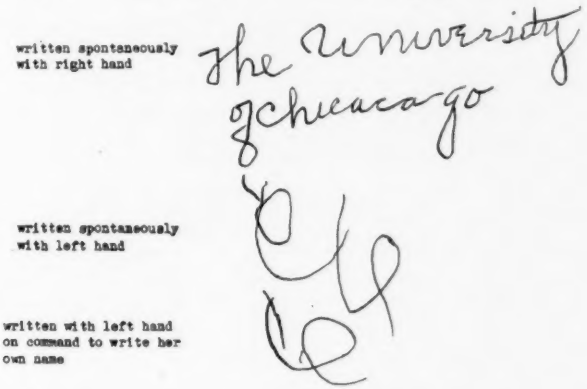

Fig. 2.—The right hand reduplicates the syllable *ca* and writes *q* for *g* in *chicacaqo*. With the left hand only meaningless loops are formed.

Encephaloventriculography.—Although the ideomotor apraxia supposedly pointed to a lesion in the corpus callosum or the left supramarginal gyrus, such a lesion would not account for the moderate hydrocephalus. The diagnosis of hemangioblastoma of the cerebellum was considered. Such a tumor would cause the patient's unsteady gait, and hemorrhage might well develop in it which would account for the sudden onset of her symptoms. It was also conceivable that a similar lesion was present in the supratentorial region. There was no angioma in the extreme periphery of the retinas to corroborate this diagnosis, but to investigate the possibility an encephaloventriculographic examination was performed. A needle was placed in the right ventricle, and then 110 cc. of cerebrospinal fluid was withdrawn from a second needle in the third lumbar interspace and replaced by air. As soon as 30 cc. of air had been injected into the lumbar needle, air began to bubble out of the open ventricular puncture needle. The roentgenograms showed moderate generalized dilatation of the entire ventricular system, including the fourth ventricle.

Course.—There was marked deterioration in the patient's mental status after this procedure. She became intermittently stuporous and unresponsive. When she was cooperative the ideomotor apraxia and apractic agraphia in her left hand persisted in undiminished degree. Figure 2 reproduces a sample of her hand-

writing at this time. Forced grasping by the right hand became pronounced. A touch on the palmar surface of the fingers of the right hand resulted in a vigorous maintained grasp which could not be released on command. The nurse had to pry objects out of her right hand. Although she tended to grasp objects placed in her left fingers and hand, there was no suggestion of forced grasping or tonic innervation when she was ordered not to grip. The ability to inhibit whatever tendency there might have been to grasp with the left hand was in striking contrast to the inability to execute commands requiring positive action with that hand. She moved both arms and both legs freely, scratching her head with either hand. There was also present now, at irregular intervals, a coarse tremor in the right hand. This was never noted when the patient was stuporous or asleep, but was exacerbated on voluntary movement of the right hand. Her performance on tests for aphasia was now inconsistent. Spontaneous speech was much reduced. Although she usually read aloud correctly, she was unable to rephrase simple sentences. When shown pictures she was often unable to describe them. At times she repeated simple oral commands but failed to execute them correctly, and at times she even gave no response at all.

A diagnosis of multiple cerebral metastases from a silent primary carcinoma was considered, but gynecologic examination, roentgenograms of the chest and a barium study of the colon did not disclose a primary tumor. Sarcomatosis of the meninges was considered a possible diagnosis. The patient was discharged to return to her home in Evanston, Ill., for further observation by Dr. Bassoe and Dr. M. H. Hobart. At home her stupor became more continuous and progressed to coma; she died eight days later, on Oct. 28, 1938.

Autopsy.—Dr. Hobart arranged with Dr. E. L. Benjamin, pathologist at the Evanston Hospital, for a complete postmortem examination, which was performed two hours after death. Dr. Benjamin has permitted me to record here the anatomic diagnoses: (1) moderate atherosclerosis of the aorta, medium-sized blood vessels and coronary arteries, and one atherosclerotic plaque on the left internal carotid artery, opposite the optic chiasm; (2) primarily contracted kidneys; (3) cholecystolithiasis; (4) submucous leiomyoma of the uterus; (5) polyp of the cervix, and (6) pulmonary aspiration of gastric contents.

On opening the skull, a yellowish discoloration was seen in the dura mater of the left anterior cranial fossa, in the leptomeninges on the inferior surfaces of both frontal lobes and on the superior surface of the corpus callosum. Aside from the left internal carotid artery, the blood vessels at the circle of Willis and over the convex surfaces of the brain seemed normal. Except for the discolorations noted, the leptomeninges also appeared normal; there was no fresh blood in them anywhere. Dr. Benjamin gave me the brain for further examination.

The brain was fixed in a dilute solution of formaldehyde U. S. P. (1:10) and then cut into coronal sections, 4 mm. thick. These revealed an aneurysm of the left anterior cerebral artery in an unusual position, far anterior to the circle of Willis, beneath and projecting up into the genu of the corpus callosum. The aneurysm plus old coagulated blood surrounding it formed a mass measuring 1.2 cm. superoinferiorly by 0.6 cm. anteroposteriorly by 0.7 cm. transversely. When the brain was viewed from the basal surface the aneurysmal mass could not be seen, since so much of it lay within the genu.

Beginning 1 cm. from the anterior end of the genu and extending backward for 4.5 cm., there was a softening in the body of the corpus callosum. In its anterior

1 cm. the softening was confined exclusively to the right half of that structure (fig. 3 *A*), but in its next centimeter it lay centrally and in the left half thereof, gradually shifting to the left in sections further posteriorly, until in the same coronal plane as that of the medial portions of cortical areas 4 and 6 it lay principally in the left half of the corpus callosum (fig. 3 *B*). It occupied this position for the remainder of its extent. Figure 4 shows the extent of the softening in the horizontal plane. In all sections through the lesion it involved almost the entire thickness of the corpus callosum.

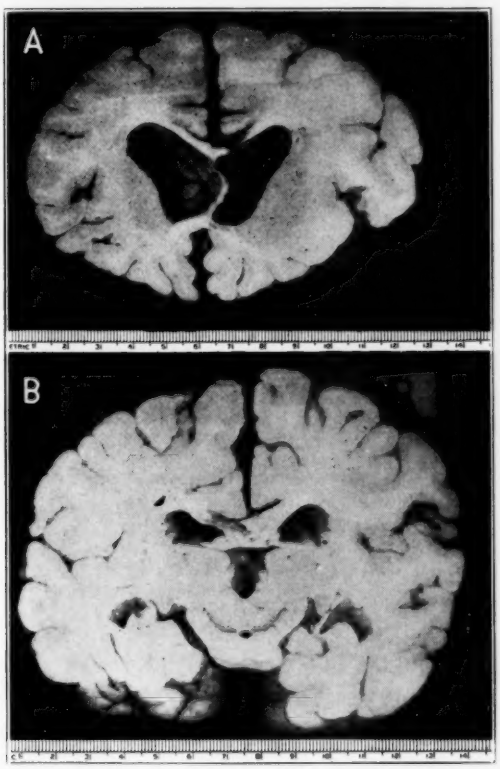

Fig. 3.—*A*, section 2 cm. behind the anterior end of the corpus callosum. Softening and thinning of the right side of the corpus callosum are visible.

B, section 7 cm. behind the anterior end of the corpus callosum. The softening is principally in the left side of that structure.

Microscopic examination of all of these sections confirmed the gross description of the extent of the softening, showed that the pathologic areas consisted of masses of macrophages laden with yellow pigment and of a few lymphocytes, and revealed in preparations stained by the Weil method areas in which the myelin sheaths showed varicose swellings lateral to the areas of complete destruction. Such swellings on the white fibers extended a maximum of not more than 5 mm. lateral to the gross lesion into the white fibers overlying the body of the left lateral ventricle. Except for an ischemic cell change in some large pyramidal cells of

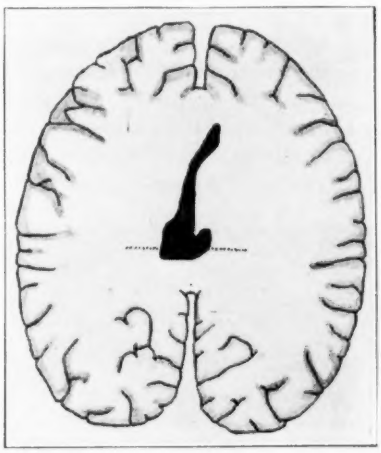

Fig. 4.—Diagrammatic horizontal section at the level of the corpus callosum. The area in solid black indicates precisely the horizontal extent of the softening in the body. The stippled black line indicates the coronal plane of the section shown in figure 5.

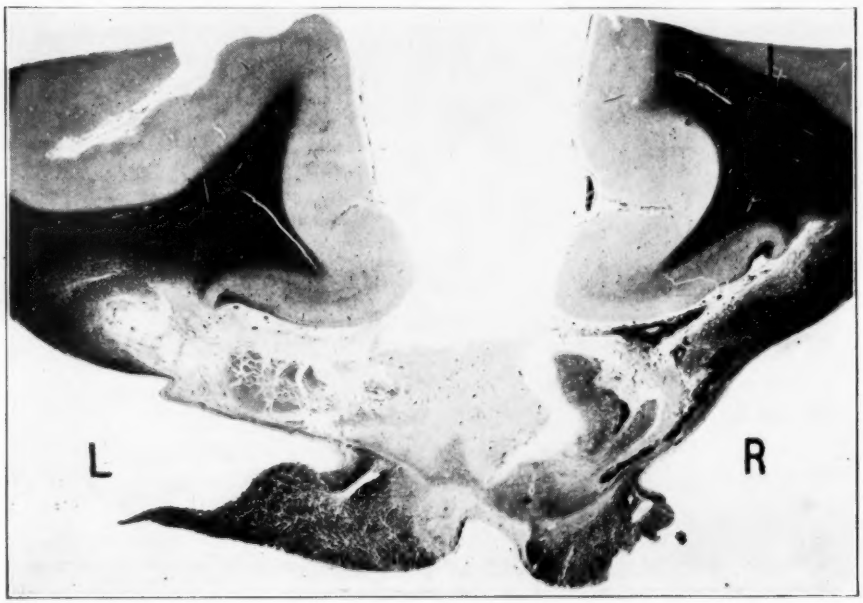

Fig. 5.—Section through the gyrus cinguli, corpus callosum and columns of the fornix in a coronal plane passing through the postcentral gyri. The original section was much larger, but the portion shown here contains all the demyelinated area. Weil stain; × 4.

layer 3 of the gyrus cinguli, the cortex was normal. In particular, no abnormality was observed in sections from numerous blocks taken through areas 4, 6 and 8 on each side and from areas 40 and 39 (supramarginal and angular gyri, respectively) on the left side, and the basal ganglia and thalamus were normal.

In addition to the foregoing extensive softening in the corpus callosum, there were two other areas of destruction of the corpus callosum. About one third of the fibers of the genu had been destroyed by the aneurysm itself (fig. 6), and a softening through the full thickness of the right half of the rostrum extended for 2.1 cm. (its entire length). There were five other minute softenings. Two of these lay in the white matter of the anteroinferior portion of the gyrus cinguli, on either side of the aneurysm below the genu of the corpus callosum (fig. 6). That on the right side was 8 mm. in diameter and that on the left side 6 mm. The other three softenings were in the right occipital lobe—one 3 and another 1 mm. in diameter in the white matter of a small unnamed gyrus immediately anterior to the posterior termination of the calcarine fissure on the superolateral surface

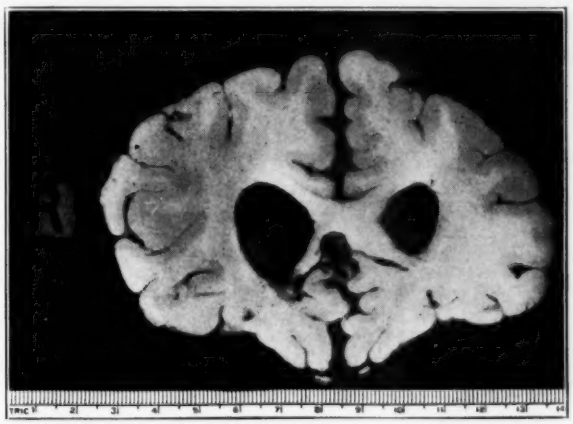

Fig. 6.—Section 0.2 cm. behind the anterior end of the corpus callosum. The aneurysm extends up into the substance of the genu. A softening in the infracallosal portion of the right gyrus cinguli is visible.

of the brain, and the last 4 mm. in diameter in the white matter lateral to the posterior horn of the right lateral ventricle. Histologically, the softenings were all like that in the corpus callosum. On account of their small size and their location in areas having no known relation to the patient's symptoms, they are not considered in the comments that follow.

The thin-walled, unruptured aneurysm was held together only by fibrous tissue at one point, external to which there was much old blood pigment in the meshes of a thick collar of surrounding fibrous tissue. Several smaller arteries around the aneurysm had intimal thickenings extending into their lumens. There were no inflammatory cells in the media of any of the arteries to suggest a syphilitic origin for the aneurysm. Only one anterior cerebral artery, the left, ran above the corpus callosum, and this contained an intimal thickening occluding about one third of its lumen, but in each callosomarginal sulcus was a large normal artery, by way of which each gyrus cinguli was apparently adequately supplied.

The leptomeninges contained many macrophages laden with blood pigment. This was most pronounced along the medial surface of each hemisphere above the corpus callosum, but was also marked in the sulci on the superolateral surface of each hemisphere. The middle cerebral arteries and their branches were normal.

Sections from some forty large pyroxylin blocks through all parts of the brain, stained by the methods of Nissl and Weil, revealed no other abnormalities.

Comment.—The clinical cases that have formed the basis for conclusions regarding the function of the corpus callosum have fallen in the past mainly into two groups: (1) those with thromboses of the anterior cerebral artery or one of its posterior branches, and (2) those with invasive neoplasms. In the former group the softening which develops includes not only the corpus callosum but also a portion of the medial surface of one cerebral hemisphere, and in the latter group the damage is never confined to the corpus callosum. A search of the literature on aneurysm of the anterior cerebral artery (materially assisted by the review of McDonald and Korb [1]) revealed, among the 60 cases reported, none in which softening of the corpus callosum formed a localized lesion in the brain post mortem. In almost all the 9 cases of isolated lesions of the corpus callosum collected from the literature by Mingazzini and Ciarla,[2] other large local focal lesions elsewhere in the brain were shown. Hence, the present case seems to be unusual in offering an opportunity to study the effect of a lesion confined to this principal commissure, although the moderate hydrocephalus, rather than other focal lesions, complicates the case.

In a case of thrombosis of the posterior branches of the left anterior cerebral artery in which there was softening of the white matter of the left gyrus cinguli, paracentral lobule, posterior part of the superior frontal gyrus and left half of the anterior three fourths of the corpus callosum, Liepmann and Maas [3] decided that the clinical symptoms of apraxia and agraphia involving the left side were due to the lesion in the corpus callosum. However, they stated that the question of the significance of the gyrus cinguli for eupraxia must remain open. In their case the condition was complicated by paralysis of the right side, which was attributed to another softening in the left internal capsule. In the cases of van Vleuten [4a] and Hartmann,[4b] however, in which

1. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. **42**:298-328 (Aug.) 1939.

2. Mingazzini, G., and Ciarla, E.: Klinischer und pathologisch-anatomischer Beitrag zum Studium der Apraxie, Jahrb. f. Psychiat. u. Neurol. **40**:24-98, 1920.

3. Liepmann, H., and Maas, O.: Fall von linksseitiger Agraphie und Apraxie bei rechtsseitiger Lähmung, Berl. klin. Wchnschr. **1**:757-758, 1907.

4. (*a*) van Vleuten, C. F.: Linksseitige motorische Apraxie, Allg. Ztschr. f. Psychiat. **64**:203-239, 1907. (*b*) Hartmann, F.: Beiträge zur Apraxielehre, Monatschr. f. Psychiat. u. Neurol. **21**:97-118 and 248-270, 1907.

tumors of the central white matter including the corpus callosum had been accompanied by apraxia on the left side, the right limbs were not paralyzed and executed commands correctly. This demonstrated clearly that the failure to perform properly on the left side was due not to inability to understand the command, but to interruption in the transmission of the impulses from the areas responsible for the understanding to areas responsible for the execution—i. e., there was ideomotor (ideokinetic) apraxia. Goldstein [5] added a case of occlusion of a posterior branch of the right anterior cerebral artery in which the lesion in the corpus callosum and neighboring right hemisphere was seen at autopsy to be similar to that in the corpus callosum and adjoining left hemisphere in the case of Liepmann and Maas. In Goldstein's case the right limbs moved normally, but there were severe apraxia and agraphia of the left hand. The similarity in the behavior of the left hand in the 2 cases indicated that the destruction of the white matter of the right gyrus cinguli in Goldstein's case was not responsible for the apraxia. These clearcut studies, made thirty years ago and subsequently confirmed by others, sufficed to convince most neurologists that an extensive lesion of the corpus callosum produced ideomotor apraxia involving the left side in a right-handed person, and Critchley [6a] and Baldy [6b] described the symptom as one of those typically encountered in cases of occlusion of the anterior cerebral artery. However, a trend away from precise localization of the various functions associated with language has later occurred. Thus, Weisenburg and McBride,[7] in their extensive monograph, concluded:

> [In] much of the modern work on apraxia and agnosia . . . the authors . . . base their conceptions on artificial differentiations of cerebral "centers" and connecting intracerebral tracts. It has been shown that such classification has no basis either in the results of psychological examinations or in definite knowledge of intracerebral fiber connections.

The present case, in which there was virtually no aphasia at the time of onset of the apraxia, would seem ample confirmation of the idea expressed by Liepmann and Maas that the structural mechanism, or "center," for understanding what is involved in the execution of a verbal command is in the dominant hemisphere and that when the intra-

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5. Goldstein, K.: (*a*) Zur Lehre von der motorischen Apraxie, J. f. Psychol. u. Neurol. **11**:169-187 and 270-283, 1908; (*b*) Der makroskopische Hirnbefund in meinem Falle von linksseitiger motorischer Apraxie, Neurol. Centralbl. **28**:898-906, 1909.

6. (*a*) Critchley, M.: The Anterior Cerebral Artery, and Its Syndromes, Brain **53**:120-165, 1930. (*b*) Baldy, R.: Les syndrômes de l'artère cérébrale antérieure, Paris, Jouve & Cie, 1927.

7. Weisenburg, T., and McBride, K. E.: Aphasia: A Clinical and Psychological Study, London, Oxford University Press, 1935.

cerebral fiber connections between the hemispheres are interrupted apraxia develops in the limb controlled by the subordinate hemisphere.

My patient also had severe agraphia of apractic type on the left side. The term apractic agraphia was coined by Heilbronner [8] to describe the disturbance in writing due to inability to make the appropriate movements despite adequate strength and coordination of the limb and standing of the movements required. In his case, paralysis of the opposite upper limb precluded a positive statement that there was the requisite understanding. Herrmann and Pötzl [9] (page 31) denied the existence of apractic agraphia; they expressed the opinion that agraphia is a generalized disturbance, in contradistinction to apraxia, which is usually confined to individual parts of the body. They cited the second case of Pelz [10] as bearing out this point of view. The patient had bilateral agraphia, but the apraxia was virtually confined to the left side. Both Sittig [11a] and Nielson [11b] have reviewed the question critically and have demonstrated unequivocally that apractic agraphia, as well as aphasic agraphia, occurs. The cases which prove decisively the existence of apractic agraphia are those in which the disability was unilateral and the opposite side was nearly normal. To the cases of Pitres,[12a] Maas,[12b] Goldstein and Sittig [11a] (F. J., pages 207 to 213) the present case is to be added. The conception of Sittig and of Nielson that agraphia may have both an apractic and an aphasic component is supported by the evidence in this case (fig. 2). The right hand writes "chicacaqo"—a perseveration of the second syllable and a substitution of "q" for "g," constituting a mild form of aphasic agraphia similar to that in Sittig's case (A. T., page 220) and Nielson's case 37 (page 109). The left hand can write only meaningless circles; the agraphia here is apractic.

Since the lesion in the corpus callosum was so extensive in my case, it is of no assistance in deciding between the contentions of Liepmann [13a]

8. Heilbronner, K.: Ueber isolierte apraktische Agraphie, München. med. Wchnschr. **53**:1897-1901, 1906.

9. Herrmann, G., and Pötzl, O.: Ueber die Agraphie und ihre lokaldiagnostischen Beziehungen, in Abhandlungen aus der Neurologie, Psychiatrie, Psychologie und ihren Grenzgebieten, Berlin, S. Karger, 1926, no. 35.

10. Pelz, A.: Zwei Fälle von apraktischer Agraphie, Ztschr. f. d. ges. Neurol. u. Psychiat. **19**:540-576, 1913.

11. (*a*) Sittig, O.: Ueber Apraxie: Eine klinische Studie, in Abhandlungen aus der Neurologie, Psychiatrie, Psychologie und ihren Grenzgebieten, Berlin, S. Karger, 1931, no. 63. (*b*) Nielson, J. M., and FitzGibbon, J. P.: Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization, Los Angeles, Los Angeles Neurological Society, 1936.

12. (*a*) Pitres, A.: Considérations sur l'agraphie (agraphie motrice pure), Rev. de méd. **4**:855-873, 1884. (*b*) Maas, O.: Ein Fall von linksseitiger Apraxie und Agraphie, Neurol. Zentralbl. **26**:789-792, 1907.

13. (*a*) Liepmann, H.: Apraxie, Ergebn. d. ges. Med. **1**:516-543, 1920. (*b*) Kleist, K.: Gehirnpathologie vornehmlich auf Grund der Kriegserfahrungen, Leipzig, Johann Ambrosius Barth, 1934.

(page 536) and Kleist [13b] (pages 476 to 483). The former maintained that the fibers destroyed in the production of the apraxia pass from the left to the right frontal lobe, and the latter expressed the opinion that the fibers pass from the left supramarginal gyrus to the opposite side. Mingazzini and Ciarla stated the belief that complete lesions of the anterior third of the corpus callosum cause apraxia of the face, whereas lesions of the middle third cause apraxia of the arm. In my case the lesion involved most of the anterior third as well as all of the middle third, but there was no facial apraxia. Mingazzini and Ciarla cited similar cases (Marchiafava and Bignami; Milani; Rossi) in which much, but not all, of the anterior third of the corpus callosum was destroyed and yet there was no faciolingual apraxia. Probably the remaining fibers in the anterior third conducted enough impulses to prevent the apraxia from appearing clinically. The fact that in my case the upper limb became apractic only after the ventriculographic study also suggests that practically all of the callosal fibers to an area must be destroyed before the ordinary tests reveal the presence of such a defect, since much of the callosal softening in my case must have existed prior to taking the ventriculogram. Foerster [14] (page 952) stated that he had divided the corpus callosum in man from before backward for 6 to 7 cm., and also from behind forward for a considerable distance without producing apraxia. This indicates not only that all of the fibers concerned with eupraxia to an area must be destroyed before apraxia appears, but also that those to any one area are spread out through much of the corpus callosum—probably those to the face and tongue occupying more than the anterior third thereof. Dandy [15] (page 50) stated: "The entire length of the corpus callosum has been divided during the course of operations on human beings . . . without the slightest suggestion of apraxia." As evidence that the surgeon may overestimate what he has accomplished at operation, I may cite case 1 in an article by Dandy,[16] in which he stated: "The corpus callosum was split to the great vein of Galen." Figure 10 in his article shows a small opening in the corpus callosum ending several centimeters anterior to what must have been the anterior extremity of the vein of Galen. It is possible that the minimal dysarthria displayed by my patient represented mild laryngo-palatolingual apraxia, of the type which in a case of Bailey's [17] caused

14. Foerster, O., cited by Lange, J.: Agnosien und Apraxien, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, pp. 807-960.

15. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1.

16. Dandy, W. E.: Congenital Cerebral Cysts of the Cavum Septi Pellucidi (Fifth Ventricle) and Cavum Vergae (Sixth Ventricle): Diagnosis and Treatment, Arch. Neurol. & Psychiat. **25**:44-66 (Jan.) 1931.

17. Bailey, P.: Tumor of the Septum Lucidum and Corpus Callosum Causing Apraxia, Arch. Neurol. & Psychiat. **22**:614-616 (Sept.) 1929.

total inability to speak and inability to swallow unless food was placed in the back of the mouth.

Although in many cases reported a severe mental deficit has been associated with lesions of the corpus callosum, I am unable in my case to be certain that the reduction in this sphere was not fully explained by the repeated subarachnoid hemorrhages, moderate hydrocephalus, increased intracranial pressure and repeated pneumencephalographic studies.

The patient's forced grasping or tonic innervation in the right hand may next be considered. Janischewsky [18a] and Bucy [18b] have each pointed out that in the presence of marked internal hydrocephalus this sign is of little localizing value, especially when it is bilateral. But in my case it appeared early and was unilateral and the patient had only moderate hydrocephalus, so one must account for it on the basis of a focal lesion. Adie and Critchley,[19] in their analysis of cases in which autopsy was done, have demonstrated that the sign may be present when a lesion involves only the frontal lobe and not the corpus callosum, and that damage to the posterosuperior portion of the frontal lobe is most likely to produce the condition. This has been subsequently confirmed and localized more exactly in experimental work on primates, and the observation of Richter and Hines [20] on macaques that excision of Brodmann's area 6 produces the "grasp reflex" has been repeatedly confirmed and extended to chimpanzees in the laboratories of Prof. J. F. Fulton [21] (page 441). The possibility of the corpus callosum playing a role in the production of forced grasping seems to have been ruled out experimentally by Kennard and Watts,[22] who not only did not find forced grasping when the corpus callosum was sectioned in the intact macaque but showed that in a unilateral or bilateral premotor preparation from which forced grasping had disappeared section of the corpus callosum did not cause the symptom to return. It is difficult to conceive how damage to interhemispheric fibers of the corpus callosum in the case reported here could possibly cause forced grasping in the right hand

18. (*a*) Janischewsky, A.: Un cas de maladie de Parkinson avec syndrome pseudobulbaire et pseudo-ophthalmoplégique, Rev. neurol. **17**:823-831, 1909. (*b*) Bucy, P. C.: Reflex-Grasping Associated with Tumours Not Involving the Frontal Lobes, Brain **54**:480-491, 1931.

19. Adie, W. J., and Critchley, M.: Forced Grasping and Groping, Brain **50**: 142-170, 1927.

20. Richter, C. P., and Hines, M.: The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Research Nerv. & Ment. Dis., Proc. (1932) **13**:211-224, 1934.

21. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

22. Kennard, M. A., and Watts, J. W.: The Effect of Section of the Corpus Callosum on the Motor Performance of Monkeys, J. Nerv. & Ment. Dis. **79**:159-169, 1934.

only; hence I do not consider the findings in this case contradictory to those of Kennard and Watts in the macaque. Had the forced grasping been present in the left hand, one might have postulated an inhibitory influence of the dominant left hemisphere over the right. In my case it is, of course, impossible to say from which cortical area the damaged fibers came, but the lesion cannot be said to involve more than the most medial uncrossed fibers from any projection on the left side; I conclude therefore that damage to these medial fibers caused the forced grasping to appear in the right hand. If this is correct, then this sign may be the first localizing sign to indicate that a tumor in one hemisphere has invaded the other hemisphere by way of the corpus callosum, and its appearance will indicate to the neurosurgeon that there is little use in trying to remove the tumor from the hemisphere first involved. Marked internal hydrocephalus with increased intracranial pressure makes the sign of no localizing value, and, as demonstrated by Walshe and Robertson's [23] case 5, a medially situated meningioma (or other tumor) may cause forced grasping from pressure on the less involved hemisphere. However, these causes for the appearance of the forced grasping would be demonstrated by pneumencephalograms. The presence of this sign, then, in conjunction with the results of air studies, might save a patient with intracranial neoplasm from a needless osteoplastic craniotomy. One such case has occurred recently in Dr. Bailey's service, that of a man (A. H.) with bilateral forced grasping in whom this sign on one side was the only evidence of involvement of the opposite hemisphere. Pneumencephalographic study as well as the bilateral forced grasping indicated that the tumor had invaded the corpus callosum. The patient was not operated on, and the clinical diagnosis of a glioma of the corpus callosum was confirmed at autopsy, several months later.

The tremor in the right upper limb in my case, which was present irregularly after the second pneumencephalogram and was exacerbated by voluntary movement, deserves passing mention, even though it occurred only at a time when the patient's general level of neurologic performance was poor. Schuster and Pinéas [24] have collected numerous cases in which unilateral forced grasping and "polymorphic hyperkinesias" were present in the same limb. In the case of van Vleuten a tremor on the right side, identical in type with that in my case, accompanied by forced grasping on the same side and apraxia on the left, was found in association with a glioma located principally in the left half of the corpus callosum and left gyrus cinguli.

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23. Walshe, F. M. R., and Robertson, E. G.: Observations upon the Form and Nature of the "Grasping" Movements and "Tonic Innervation" Seen in Certain Cases of Lesion of the Frontal Lobe, Brain **56**:40-70, 1933.

24. Schuster, P., and Pinéas, H.: Weitere Beobachtungen über Zwangsgreifen und Nachgreifen und deren Beziehungen zu ähnlichen Bewegungsstörungen, Deutsche Ztschr. f. Nervenh. **91**:16-56, 1926.

The clinical course of the case of aneurysm just described, which suggested neoplasm as the most likely diagnosis, is paralleled in many respects by a case occurring in the service of Prof. H. Cairns, Nuffield professor of surgery at Oxford University, by whose permission it is included in this report.

CASE 2.—*History.*—E. D., a female domestic servant aged 33, entered the service of Prof. H. Cairns at the London Hospital on March 11, 1931, having been referred by Dr. Lister, of Plymouth, England. Six months previously there had appeared bouts of diplopia, each lasting only a "minute or so," but recurring at least once a day for the next four months. Two months after the diplopia began there was an episode of shaking of the right leg of two to three minutes' duration, which came on while the patient was walking. She said that it felt as though she "were standing on a nerve." This never recurred. Headaches, previously present only before the menstrual flow, had increased moderately in severity and frequency for one year. Two months before entry she suddenly had a sensation of something coming over her head, and fell to the floor unconscious for fifteen minutes. When she regained consciousness she could not see at all for several minutes; however, sight suddenly returned, on both sides at once, although there was photophobia. She vomited many times that night and had an excruciating constant occipital headache, extending down the back of the neck on both sides: this gradually diminished during the course of three weeks. Then, after a day of severe pain in the right temple, she had a sensation as if knives and daggers were passing through her head and lost consciousness for half an hour. When she recovered consciousness she vomited again and had a severe headache, which gradually diminished during the next four weeks. Dr. Lister found slight hypalgesia over the area of distribution of the first and second divisions of the right trigeminal nerve shortly after the second attack of unconsciousness, but this had disappeared two weeks later. For one week before entry she saw "a little fluff" in the right eye, which moved with the eye. Ever since the first attack of unconsciousness she had had "throbbing" noises in the right temporal region of the head, and there had been occasional pricking sensations in both hands, lasting two to three minutes at a time. There had been amenorrhea for the past two months.

Examination.—Abnormal findings in a complete neurologic examination were: (1) bilateral papilledema 3 D. in the right eye and 2 D. in the left, numerous flame-shaped hemorrhages around both disks, a very large hemorrhage between the disk and the macula on the right side, and bilateral venous engorgement; (2) incongruous left lower quadrantic homonymous hemianopia on the day of entry, which was nearly gone two days later, and right cecocentral scotoma corresponding to the hemorrhage; (3) visual acuity, 6/24 in the right eye and 6/6 in the left; (4) tenderness on firm pressure in the lateral portion of the right occipital region; (5) slight weakness of the left side of the face; (6) diminished left lower abdominal reflex; (7) very slight hypalgesia in the left limbs and left side of the trunk, and (8) diminished proprioception in the left great toe on one occasion.

Roentgenograms of the skull revealed a few areas of diminished density in the right parietal bone just in front of the lambdoid suture and a well marked meningeal channel in the posterior part of the right parietal bone, with no similar groove on the opposite side.

Course.—The symptoms and signs pointed principally to a right parieto-occipital neoplasm, and the roentgenograms suggested that it was a meningioma. A ventriculogram revealed dilated lateral and third ventricles, but the right lateral

ventricle was less dilated than the left and had a shorter posterior horn; right posterolateral osteoplastic exploration gave negative results. A subtemporal decompression was made. In the last half of the first postoperative week the patient began to complain of numbness in the left hand and of releasing objects from the hand without realizing it. This disappeared in two weeks. During her further convalescence, unsteadiness of gait, a tendency to fall backward in the Romberg position and inability to walk tandem were all sufficiently pronounced to give rise, in conjunction with the roentgenographic demonstration of dilatation of the lateral and third ventricles, to the speculation that the patient might have a midline lesion in the posterior fossa. Within another two weeks, however, the patient improved to the point at which 6/12 vision in the right eye and the preretinal hemorrhage in the right fundus were the only abnormal vestiges of the previous signs and symptoms. In his final letter to Dr. Lister reviewing the case, Professor Cairns concluded that an aneurysm at the base of the brain on the right side was the most probable diagnosis. This conclusion was borne out two and a half years later. In the interim the patient had been healthy, but she was found unconscious on the floor one morning and died shortly thereafter. Dr. W. A. D. Kind, of Paignton, England, the general practitioner who saw her at this time, performed an autopsy, which disclosed a pea-sized aneurysm of one of the posterior vessels on the right side of the circle of Willis, and extensive hemorrhage throughout the subarachnoid space therefrom.

GENERAL COMMENT

Difficult to explain in the 2 cases was the moderate degree of hydrocephalus that was present. Encephaloventriculograms in the first case proved the presence of a communication between the subarachnoid space and the fourth ventricle, ruling out "obstructive hydrocephalus." Strauss, Globus and Ginsburg [25] stated that in their postmortem material internal hydrocephalus was not infrequent in cases of spontaneous subarachnoid hemorrhage due to intracranial aneurysm. They said that it is "very likely due to partial obliteration of the subarachnoid space by organizing hemorrhage." They mentioned no actual microscopic or gross preparations showing such obliteration, and in my first case the leptomeninges seemed normal grossly. However, the microscopic examination in my first case showed numerous areas of congestion of the leptomeninges, with phagocytic cells laden with blood pigment. The presence of bilateral papilledema in both the cases reported here might be regarded as further evidence that there was a chronic increase in intracranial pressure.[26] I agree that the cellular reaction in the leptomeninges is the probable cause of the hydrocephalus.

25. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **27**:1080-1132 (May) 1932.

26. On the other hand, it is known that papilledema with retinal hemorrhages may occur after subarachnoid hemorrhage into the sheath of the optic nerve without any rise of intracranial pressure (Riddoch, G., and Goulden, C.: Brit. J. Ophth. **9**:209-233, 1925).

In the clinical study of the present cases I originally believed that the presence of bilateral papilledema accompanied by progression in symptoms pointed to neoplasm rather than to primary vascular disease, despite the sudden increase in severity of symptoms. It is well known that papilledema develops with an aneurysm which has grown so large that it becomes a significant space-occupying mass, and that immediately after a spontaneous subarachnoid hemorrhage papilledema may be present, which recedes in a few weeks. Dott [27a] and Jefferson [27b] have each pointed out recently that aneurysms at the base of the brain may cause defects in the visual fields suggesting tumor. However, attention has been called only infrequently to cases in which a small aneurysm has simulated a tumor as a result of obstruction to the flow of cerebrospinal fluid and/or to repeated small bleedings, as in the present cases.

Six cases similar to these have been found in a partial review of the literature. Strauss, Globus and Ginsburg [25] have reported 2 of them. The patient in their case 12 (page 1,105) had had intermittent headaches for two years, at first mild but for six months more severe and localized in the frontal region. One week before admission stiffness of the neck and a severe pain in the back developed suddenly and were followed by several generalized convulsions. Examination revealed bilateral papilledema, nuchal rigidity and a bilateral Kernig sign. The xanthochromic spinal fluid was under an initial pressure of 340 mm. of water. An encephalogram showed dilated lateral ventricles and was therefore followed by a suboccipital craniectomy, which revealed nothing abnormal. The patient was readmitted two and a half months later; her headaches had become more severe and constant, but the papilledema had subsided slightly. She died after a ventriculographic examination, and autopsy showed an unruptured aneurysm at the origin of the left posterior cerebral artery, filling the posterior part of the third ventricle. The patient in their case 35 (page 1121) five months before entry had suddenly vomited at the onset of a severe headache, which lasted one week. One month later, and again nine days before entry, there were similar attacks, with radiation of pain down the spine during the last attack. On examination the patient was apathetic and at times psychotic, had bilateral papilledema, a bilateral Kernig sign, nuchal rigidity and paresis of both internal rectus muscles. A ventriculogram revealed symmetric internal hydrocephalus. Thirty-five days later the patient had improved markedly, the papilledema being just discernible, and the diagnosis of intracranial aneurysm rather than of tumor was considered established.

27. (*a*) Dott, N. M.: Intracranial Aneurysms: Cerebral Arterio-Radiography; Surgical Treatment, Edinburgh M. J. **40**:219-240, 1933. (*b*) Jefferson, G.: Compression of the Chiasma, Optic Nerves and Optic Tracts by Intracranial Aneurysms, Brain **60**:444-497, 1937.

In Fearnsides'[28] case 4, minor hemorrhages from an aneurysm of the anterior cerebral artery had produced intermittent bouts of headache for months, with bilateral papilledema. In Booth's[29] case, small hemorrhages into the left frontal lobe from an aneurysm had caused generalized convulsions without focal character for seventeen months, with severe papilledema. In Wallesch's[30] case 3, the illness ran a slow progressive course, with repeated bleedings, and at autopsy a large mass of reddish brown blood was observed in the cisterna chiasmatis, with hydrocephalus of the first three ventricles. The hydrocephalus, which was thought by Wallesch to be due to obstruction of the aqueduct of Sylvius by the old hematoma, might also have been caused by general obstruction in the leptomeninges, as in my first case. In Sai and Costantinides'[31] case of aneurysm of the anterior cerebral artery, there was a history of progressive dementia, somnolence, impotence and increasing weight for two years. For a few months before entry there had been moderate amnesic aphasia, agraphia, right hemiparesis and disturbance in equilibrium. In an encephalogram the aneurysm appeared as a small tumor in the anterior portion of the third ventricle; it had partially obstructed the left foramen of Munro, causing enlargement of the lateral ventricle.

From these 8 cases, I point out the following as important features of aneurysms obstructing the flow of cerebrospinal fluid: (1) The obstruction is due either (*a*) to macrophages and adhesions in the subarachnoid space, caused by blood from a seeping aneurysm or (*b*) to occlusion of a foramen of Monro or the aqueduct of Sylvius by the aneurysm itself. (2) In the first group, repeated sudden accessions of disorder, usually including headache and vomiting, and at times nuchal rigidity, gradually receding, to return days or months later, may be milder than one usually associates with spontaneous subarachnoid hemorrhage. Minor degrees of bleeding occur which produce headache as the only symptom. (3) Papilledema is often accompanied by large retinal and subhyaloid hemorrhages. (4) Transitory involvement of cranial nerves may occur. (5) Moderate hydrocephalus may develop, give a progressive downhill character to the clinical history and lead to a diagnosis of neoplasm, the sudden outbursts of symptoms being erroneously explained as due to hemorrhage in the neoplasm. Symmetric hydrocephalus may give rise to the erroneous conclusion that

28. Fearnsides, E. G.: Intracranial Aneurysms, Brain **39**:224-296, 1916.

29. Booth, J. A.: An Aneurysm of the Left Anterior Cerebral Artery with Rupture, Simulating a Brain Tumor, J. Nerv. & Ment. Dis. **36**:528-533, 1909.

30. Wallesch, E.: Die Verlaufstypen der Rupturaneurysmen am Hirngrunde, Virchows Arch. f. path. Anat. **251**:107-133, 1924.

31. Sai, G., and Costantinides, C.: La diagnosi radiologica degli aneurismi del poligono de Willis, Riv. di neurol. **55**:449-469, 1932.

there is a tumor in the posterior fossa. (6) Spreading of the subarachnoid blood up onto the superolateral surface of the cerebral hemisphere or occlusion of the foramen of Monro by the aneurysm may give rise to symptoms interpreted erroneously as arising from a tumor of the hemisphere.

Particular attention should be directed to these cases of cerebral aneurysm since the walls are firmer than those of most bleeding aneurysms and an arteriographic examination for diagnosis is especially feasible in such cases. Had such a procedure been carried out in my first case it is possible that the diagnosis could have been made intra vitam and the patient's useful life lengthened by operative removal of the aneurysm.

SUMMARY

Two cases of seeping aneurysm of a cerebral artery simulating cerebral tumor are reported. In the first the aneurysm caused a softening confined almost exclusively to the corpus callosum. This lesion produced apractic agraphia and ideomotor apraxia in the left hand, and its extension into the most medial portion of the left hemisphere probably explains the forced grasping that was present in the right hand.

Forced grasping may be the first sign of invasion of the opposite hemisphere by a cerebral tumor. By a pneumencephalogram one can rule out other causes for the appearance of the sign, and thus utilize its presence to avoid unnecessary surgical procedures.

Symptoms and findings suggesting a seeping intracranial aneurysm are pointed out.

NOTE.—Since this paper was submitted for publication there has appeared a report by Van Wagenen and Herren (Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum, ARCH. NEUROL. & PSYCHIAT. **44:** 740-759 [Oct.] 1940). These workers divided the corpus callosum surgically in 10 cases in man; they state that in 5 of these cases they made a complete longitudinal transection of that structure and that in no case has any apraxia, astereognosis or gross disturbance of memory or ability to calculate or to reason appeared. If postmortem studies show that the corpus callosum was completely divided in their cases, strong evidence will be present that it is wrong to conclude that this intercerebral commissure is one of the essential links in the maintenance of eupraxia.

REPRESENTATION OF THE SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEMS IN THE FOREBRAIN OF THE CAT

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There has been much controversy as to the distribution of function of the sympathetic and parasympathetic nervous systems in the forebrain, particularly in the hypothalamus. Beattie and Sheehan [1] found these systems to be separately represented, parasympathetic effects being obtained in the anterior region of the hypothalamus (tuber cinereum) and sympathetic effects in the posterior region. Ranson and his associates,[2] however, have obtained sympathetic effects throughout the hypothalamus, including the tuber cinereum, as far forward as the optic chiasm. The only parasympathetic reaction regularly observed by them on hypothalamic stimulation was contraction of the urinary bladder, and this was found on stimulation in front of the optic chiasm. Among sympathetic effects they observed dilatation of the pupils, rise in blood pressure, secretion of epinephrine, secretion of sweat, inhibition of gastrointestinal peristalsis and erection of hair. Masserman and Haertig [3] obtained parasympathetic effects on the gastrointestinal tract from both the anterior and the posterior part of the hypothalamus provided that weak currents were used for stimulation. Ury and Gellhorn [4] have pointed out that the reflex dilatation of the pupil from

Aided by a grant from the John and Mary R. Markle Foundation.

From the Departments of Physiology and Psychiatry of the University of Illinois College of Medicine and the Institute for Juvenile Research.

1. Beattie, J., and Sheehan, D.: The Effects of Hypothalamic Stimulation on Gastric Motility, J. Physiol. **81**:218-227, 1934.

2. (*a*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467-474 (March) 1935. (*b*) Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of Points in the Forebrain and Midbrain, ibid. **34**:931-955 (Nov.) 1935.

3. Masserman, J. H., and Haertig, E. W.: The Influence of Hypothalamic Stimulation on Intestinal Activity, J. Neurophysiol. **1**:350-356, 1938.

4. Ury, B., and Gellhorn, E.: Role of the Sympathetic System in Reflex Dilatation of Pupil, J. Neurophysiol. **2**:268-275, 1939.

painful stimuli is almost entirely due to inhibition of the tone of the third nerve, and the work of Claes [5] has also given evidence of the importance of the inhibition of the parasympathetic tonus in pupillary dilatation. Darling and Darrow [6] have pointed out that a rise in blood pressure may likewise be due to inhibition of parasympathetic control.

In the present experiments we have recorded the effect of stimulation of the forebrain on certain effectors, some of which were specific indicators of parasympathetic and others of sympathetic activity. For example, dilatation of the pupil on the side on which the cervical sympathetic fibers has been cut is an indicator of parasympathetic activity via the third nerve. At first we thought that the difference between the size of the normal and that of the denervated pupil would indicate the sympathetic response, but we later found that stimulating one side of the hypothalamus did not always cause a bilaterally equal response. The indicators of sympathetic response that have here been relied on as unambiguous are the response of the nictitating membrane, the secretion of sweat and the variations in resistance and potential of the skin.

METHOD

In experiments on 34 cats of moderate size, with the Horsley-Clarke stereotaxic instrument (Horsley and Clarke [7]), the forebrain was stimulated for from one to five seconds by a Harvard inductorium fed by 3 volts (with the secondary 6 to 12 cm. from the primary) led through bipolar electrodes made of 22 and 28 gage wire insulated to the tip with bakelite.

After the experiment the brain was fixed by injecting a dilute solution of formaldehyde U. S. P. (1:10) into the carotid artery. In 19 experiments the brain was dehydrated, embedded in pyroxylin, cut at 40 microns and stained with cresyl violet. The sections were projected, drawn and compared with a standard set of photomicrographs of the cat's brain cut in the same planes. The Horsley-Clarke reading at the surface and the base of the brain and the number of millimeters traversed between being known, the anatomic position of the needle at any reading could be accurately determined in spite of slight shrinkage. In 15 experiments the brain was sectioned grossly with a microtome knife and studied.

The diameters of the pupils were photographed in about 300 instances by a moving picture camera, after the lids and nictitating membranes had been pulled back, and were measured on enlarged projections. Since it was found that the size of the pupils could be estimated to within 1 mm. of that recorded, the agreement of two experimenters as to size was often used in lieu of photographs.

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5. Claes, E.: Contribution à l'étude physiologique de la fonction visuelle: Activités pupillo-motrices du diencéphale et du mésencéphale chez le chat non anesthésié, Arch. internat. de physiol. **48**:261-280, 1939.

6. Darling, R., and Darrow, C. W.: Determining Activity of the Autonomic Nervous System from Measurements of Autonomic Change, J. Psychol. **5**:85-89, 1938.

7. Horsley, V., and Clarke, R. H.: The Structure and Functions of the Cerebellum Examined by a New Method, Brain **31**:45-124, 1908.

As an indication of sweat gland activity, a galvanometer was used to record either the resistance or the potential of the foot pads between an indifferent electrode on an area where the skin had been abraded and an active electrode on the foot pads (Darrow [8]).

The amount of sweat secreted was also directly determined in some instances. A current of dry air drawn over the foot pads was passed over glass fibers coated with calcium chloride (Darrow [9]), altering their ionization and electrical resistance. The resistance of the fibers controlled the rate of build-up of condenser charges

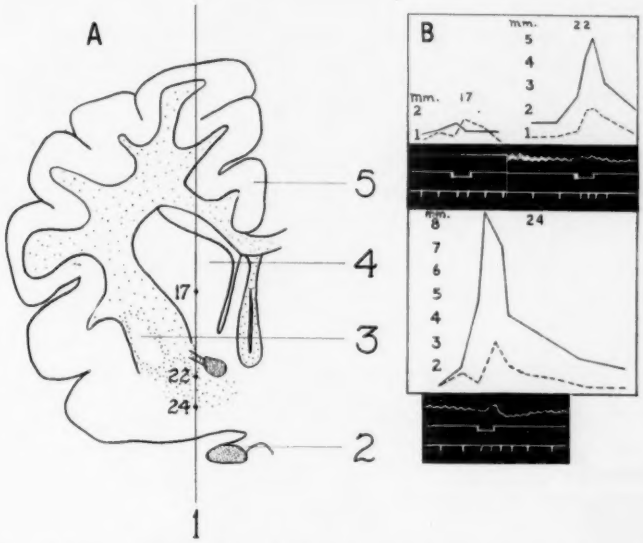

Fig. 1.—*A*, frontal section through the left side of a cat's brain (A 16.5). A 16.5 indicates the frontal plane 16.5 mm. rostral to the interaural plane, arbitrarily taken as zero for the Horsley-Clarke instrument. Compare the photomicrographs of sections of the cat's brain published in the article by Gerard, Marshall and Saul (Electrical Activity of the Cat's Brain, ARCH. NEUROL. & PSYCHIAT. **36**:675-735 [Oct.] 1936). These photomicrographs were also used in the present study. They were prepared in Dr. Ranson's laboratory. The vertical line (*1*) indicates the path of the electrode in one experiment; *2*, the optic chiasm; *3*, the globus pallidus; *4*, the caudate nucleus, and *5*, the rostral gyrus. *B*, results of the stimulation at points *17*, *22* and *24*, respectively, on the pupils and blood pressure. The heavy line indicates diameters of the left, or normal, pupil; the interrupted line, diameters of the right, or sympathectomized, pupil. Then follow: (*1*) the blood pressure curve; (*2*) the signal indicating the period of stimulation, and (*3*) the signal indicating the instant when the pupils were photographed.

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8. Darrow, C. W.: Uniform Current for Continuous Standard Unit Resistance Records, J. Gen. Psychol. **6**:471-473, 1932.

9. Darrow, C. W.: Quantitative Records of Cutaneous Secretory Reactions, J. Gen. Psychol. **11**:445-448, 1934.

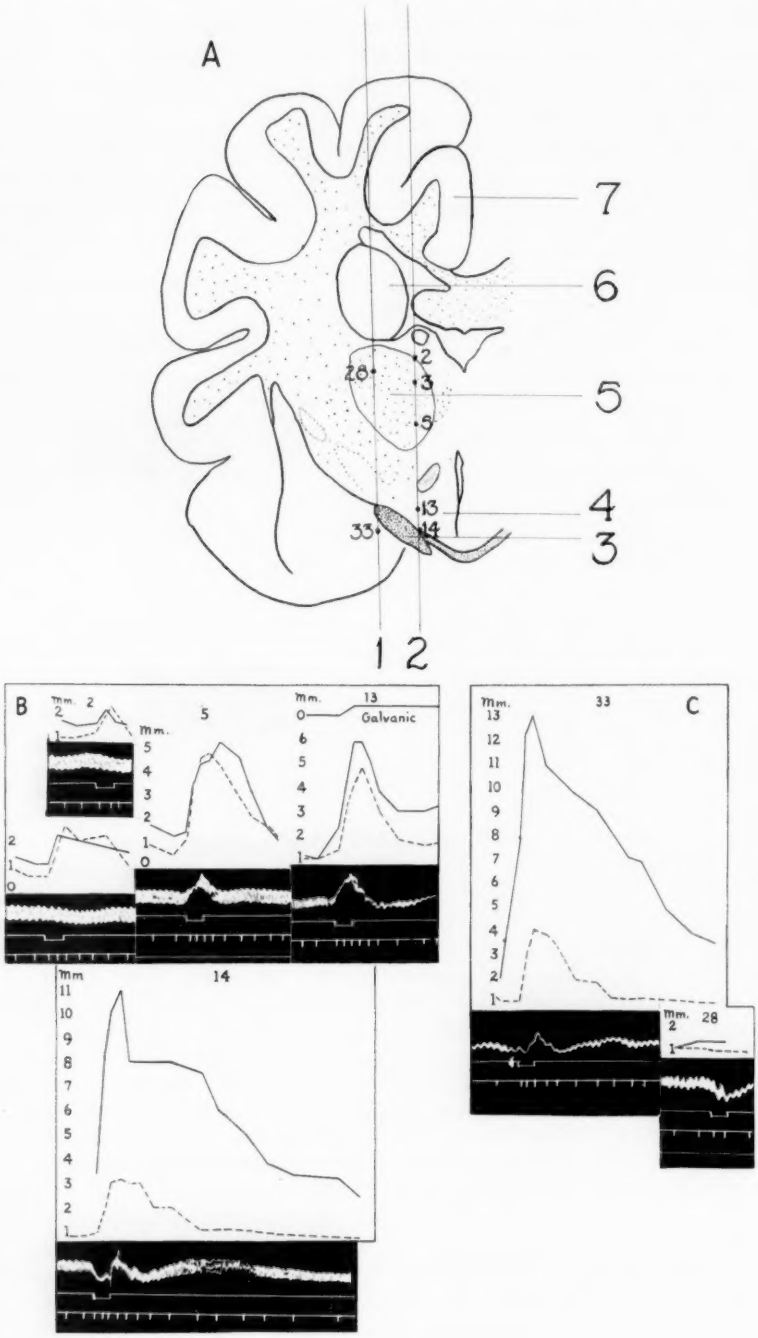

Figure 2

(See legend on opposite page)

regulating the frequency of a vacuum tube oscillator. The change in frequency of the oscillator was recorded as an indicator of sweating, along with other recorded changes, on a kymograph drum.

Blood pressure was taken from a carotid artery, measured with a Hürthle membrane manometer and recorded on the kymograph drum.

Movements were recorded from observation.

In some experiments the pupillary responses were recorded without alteration of the nerve supply; in others the cervical sympathetic fibers were cut on one side.

RESULTS

The responses obtained depended on the location of the stimulating electrode, the excitability of the animal and the strength of stimulus used. We were interested not only in the threshold responses for the various effects as studied by Ranson and his co-workers,[2] but also in the extent to which we could produce them by stimuli that were stronger and yet sufficiently localized to cause the clearcut changes in response possible with weaker stimuli with a shift of the electrode of 1 mm.

Pupils.—Without Denervation: The main response of the pupils obtained through the forebrain was one of bilaterally equal dilatation, the extent increasing as the needle descended. In responsive preparations this effect could be obtained through the corona radiata as close to the cortex as 3 mm. below the surface. This type of response was elicited mainly in the caudate nucleus, the lenticular nucleus and the thalamus. In the hypothalamus, however, the dilatation was unequal on the two sides, the ipsilateral pupil frequently dilating much more than the contralateral one (figs. 1 and 2). With the electrode in the region surrounding the optic chiasm there was bilateral constriction, and with the needle in the pretectal area there was constriction during the stimulation, followed by bilaterally equal dilatation.

Unilateral Cervical Sympathectomy: With the cervical portion of the sympathetic chain cut on one side the results were in large part similar to those in the normal animal. Stimulation of the basal ganglia still gave bilaterally equal dilatation, which increased progressively as the electrode descended, indicating that the stimuli induced inhibition of parasympathetic control of varying degree. When the hypothalamic region (supraoptic nucleus, anterior hypothalamic area,

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EXPLANATION OF FIGURE 2

A, frontal section through the left side of the cat's brain (A 13.6). *1* and *2* indicate the path of the bipolar electrode in one experiment; *3* denotes the optic tract; *4*, the anterior hypothalamic area; *5*, the ventral thalamic nucleus (anterior part); *6*, the head of the caudate nucleus, and *7*, the fornicate gyrus.

B and *C* (A 13-13.5), results of stimulation of the pupils, the blood pressure and the galvanic reflex. General arrangement is that in figure 1 *B*. At the left upper corner of figure 2 *B* is illustrated the effect of stimulation of point *2;* below, that of point *3*, and in the middle and at the right side, that of points *5* and *13*, respectively. The top line of tracings for point *13* represents the effect of stimulation on the galvanic reflex. The lower graph shows the effect of stimulating point *14*. In the right lower corner of *C* is shown the effect of stimulating point *28;* the other graph shows the results of stimulating point *33*.

lateral hypothalamic area, posterior hypothalamic nucleus and mamillary body) was stimulated, however, we found in several instances that the reaction on the denervated side was diminished but present, giving evidence not only of the inhibitory reaction via the third nerve but also of a diffuse sympathetic excitation throughout the hypothalamus. Not infrequently, however, it was found that the homolateral side showed a more marked dilatation of the pupil than the contralateral side. Since the hypothalamus was invariably stimulated on the left side and the result was independent of whether the cervical sympathetic fibers were cut on the left or on the right side, it follows that the inhibition of the third nerve was greater on the homolateral side. In the pretectal region there was still constriction during stimulation, followed by dilatation on both sides, indicating that in the animal with the cervical sympathetic fibers cut on one side both responses involved inhibitory effects on the parasympathetic system.

Nictitating Membrane.—A contraction of the nictitating membrane was elicited by stimulating the pretectal region, the anterior, posterior and lateral hypothalamic nuclei, the supraoptic nuclei, the mamillary bodies, and the region of the septum pellucidum. This reaction has a fairly high threshold, and a stimulus which causes the whole rage response (hypothalamic syndrome) to occur is required to elicit it. Once present, however, it is necessary only to bring the secondary of the induction coil a fraction of a centimeter closer to the primary to change the response from a minimal to a maximal one. Further, in some animals in which the level of excitability was moderately low responses could be obtained from the pupils, the blood pressure and the striated muscles but not from the nictitating membrane in any region of the brain. The nictitating membrane proved to be such a quantitatively reliable indicator of sympathetic activity that it has been used further in experiments with drugs. A preliminary report of these results has appeared elsewhere.[10]

The combination of sympathetic excitation and parasympathetic inhibition is demonstrated by recording pupillary reactions together with the contraction of the nictitating membrane on hypothalamic stimulation. An experiment in which the cervical sympathetic fibers were cut on the left side and the left mamillary body was stimulated may illustrate the results. On stimulation the right pupil dilated from 1.0 to 8.0 mm. and the nictitating membrane contracted, whereas on the left (sympathectomized) side no reaction of the nictitating membrane was observed and the pupil dilated from 1.5 to 4.0 (inhibition of the tonically innervated third nerve). However, such a reaction pattern does not occur in every case in which sympathetic discharges, as proved by the unilateral contraction of the nictitating membrane, are present. In the experiment from which the illustration just cited was chosen the normal pupil showed regularly greater dilatation than the sympathetically denervated pupil when the mamillary body or the region immediately posterior to it was stimulated. If, however, the stimulus was applied between the red nucleus and the mamillary peduncle we observed a greater pupillary dilatation on the homolateral (sympathectomized) side than on the contralateral side, although a contraction of the nictitating membrane appeared each time on the latter. Apparently, sympathetic impulses may reach the nictitating membrane without becoming effective on the pupil.

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10. Carlson, H.; Darrow, C. W., and Gellhorn, E.: Physiologic and Pharmacologic Studies on the Hypothalamus, Am. J. Physiol. **129**:329, 1940.

Sweat Secretion and Skin Potential.—Darrow [11] has shown that in the human palm sweating is directly related to skin conductance and is hyperbolically related to skin resistance. It has also been demonstrated by numerous workers that resistance and changes in potential are closely related. Records of potentials were sometimes more readily obtained from the cat than were records of resistance. The term galvanic here refers to either type of reaction. We were able to trace the galvanic changes in response to stimulation through the internal capsule into the cerebral peduncles, from there into the hypothalamus (anterior and posterior portions) and then up into the pretectal region. Directly recorded sweating responses were also traced throughout the hypothalamus and in the pretectal region, being maximal in the regions that gave the maximal response of

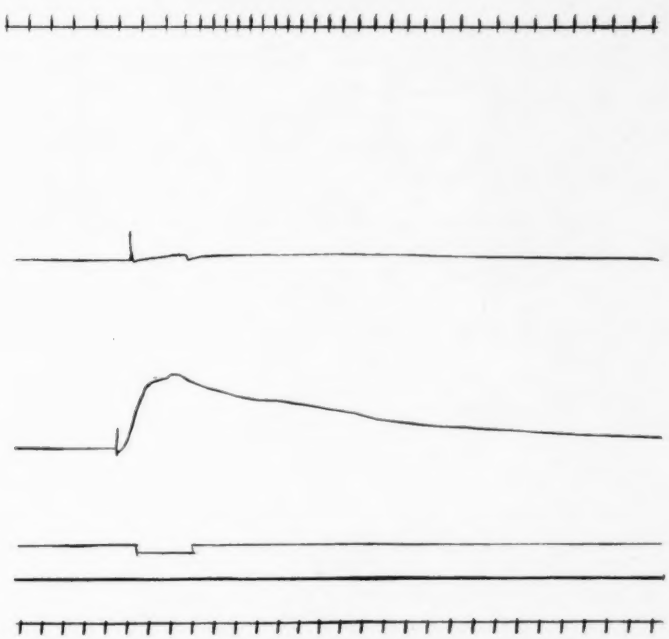

Fig. 3.—Stimulation of the posterior hypothalamic area. The top line indicates the influence on sweat secretion; the second line shows the effect on the denervated nictitating membrane, and the third line, the effect on the normal nictitating membrane; the fourth line indicates the signal of stimulation. Harvard inductorium coil; distance 8 cm.; time expressed in five second intervals (lowest line).

the nictitating membrane (fig. 3). This agrees with the accepted evidence for sympathetic innervation of the sweat glands (Darrow [12]).

Blood Pressure.—We found, as did Ranson and his associates,[2] an increase in blood pressure on stimulation of the hypothalamus and pretectal regions and a

11. Darrow, C. W.: The Significance of Skin Resistance in the Light of Its Relation to the Amount of Perspiration, J. Gen. Psychol. **11**:451-452, 1934.

12. Darrow, C. W.: Neural Mechanisms Controlling the Palmar Galvanic Skin Reflex and Palmar Sweating, Arch. Neurol. & Psychiat. **37**:641-663 (March) 1937.

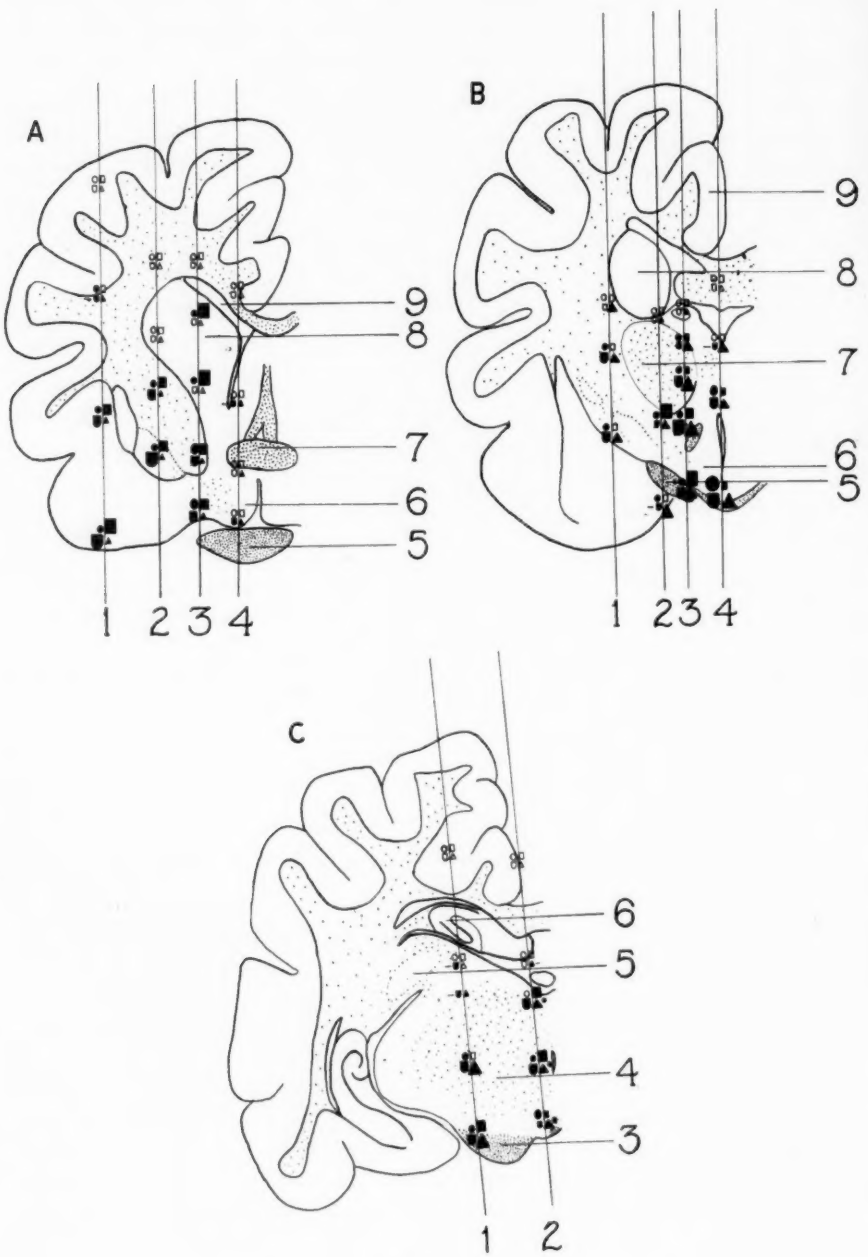

Figure 4

(See legend on opposite page)

decrease on excitation of the telencephalon (septum pellucidum and around the anterior commissure), but we usually also secured moderate increases on stimulating the thalamus. Variations in pressure with the level of excitation of the preparation will be discussed later.

Movements.—On stimulating the pyramidal tracts, we observed flexion of the contralateral forepaw or hindpaw, as did Ranson and his co-workers.[2] Throughout the hypothalamus, thalamus, caudate nucleus and lenticular nucleus there was an increase in tonus on stimulation, often accompanied by slight hunching of the back and exaggeration of tremor. In the hypothalamus, besides these reactions, there were chewing, sneezing, swallowing, salivation, pilomotor reaction, contraction of the nictitating membrane, unsheathing of the claws, twitching of the whiskers, contraction of facial muscles into a snarl and even, on several occasions, crying out.

Syndromes.—Simultaneous records of the various effects such as we have made show that various syndromes result from stimulation of the various regions. They vary to a slight extent from animal to animal (fig. 4). In the hypothalamus, if there was any response, we have found almost invariably dilatation of the pupil, contraction of the nictitating membrane, secretion of sweat, change in galvanic potential or resistance, increase in blood pressure and "rage" movements. In the pretectal regions constriction of the pupil was obtained, followed by dilatation, increase in blood pressure, contraction of the nictitating membrane, sweat secretion, galvanic response and tonic reactions. In the thalamus, our preparations varied in the reaction of the blood pressure and dilatation of the pupils to stimulation. Although the usual effect was dilatation and increased pressure, which became progressively greater as the electrode descended, there were in some cases no reaction of the pupil and decrease of blood pressure on stimulation in the upper levels, with gradual transition to slight dilatation and increased pressure as the electrode was moved toward the hypothalamus.

EXPLANATION OF FIGURE 4

Frontal sections through the left half of the cat's brain, showing the effects of stimulation of various parts of the brain as the electrode descends along lines *1, 2, 3* and *4*. Several typical experiments are represented in each plane.

The following symbols were chosen: *U*'s indicate the blood pressure response; triangles, the pupillary responses; circles, movement, and squares, the galvanic reflex.

The hollow symbols indicate no change in function. The size of the solid symbols indicates the degree of change. When the blood pressure falls, the solid *U* symbol is preceded by a minus sign. The solid triangle followed by a minus sign indicates pupillary constriction; without a minus sign it denotes pupillary dilatation. The asterisk indicates that pupillary dilatation was preceded by constriction. The sympathetic fibers were cut on one side, but no differences in pupillary dilatation resulted.

A (A 15.0-16.0), *5* indicates the optic chiasm; *6*, the anterior hypothalamic area; *7*, the anterior commissure; *8*, the head of the caudate nucleus, and *9*, the lateral ventricle.

B (A 13.0-14.0), *5* indicates the optic tract; *6*, the anterior hypothalamic area; *7*, the ventral thalamic nucleus (anterior part); *8*, the head of the caudate nucleus, and *9*, the fornicate gyrus.

C (A 5.5-6.5), *3* indicates the cerebral peduncle; *4*, the red nucleus; *5*, the lateral geniculate body, and *6*, the cornu ammonis.

COMMENT

In interpreting our results it has been necessary to use judgment in deciding to what extent this method will localize function. For example, stimulation of the descending column of the fornix in the hypothalamic area will elicit a hypothalamic syndrome, whereas stimulation of the fornix elsewhere will not. It is probable, therefore, that the hypothalamic response in the first case is due to response of surrounding areas rather than to that of the fornix. A similar situation is obtained with respect to the mamillary bodies, the optic chiasm and all other structures small enough to allow partial stimulation of the surrounding tissue. In these experiments, therefore, we have discussed the results in terms of the larger areas.

Perhaps the most striking finding in this work is the wide distribution of inhibitory reactions involving the parasympathetic system throughout the forebrain, as measured by pupillary dilatation in a cat with cervical sympathectomy. Contrary to the findings of Beattie and Sheehan,[1] who obtained parasympathetic effects from the anterior and sympathetic effects from the posterior part of the hypothalamus, and to those of Ranson and his associates,[2] who elicited much sympathetic but little parasympathetic response from the hypothalamus (except anterior to the optic chiasma), we have obtained both sympathetic excitatory responses and reactions involving inhibition of the parasympathetic third nerve throughout the hypothalamus. Although an important part of the hypothalamic syndrome is mediated by the sympathetic nervous system (sweat secretion and contraction of the nictitating membrane), the pupillary dilatation seems to be a function of inhibition of the parasympathetic (third nerve) rather than one of sympathetic excitation. When sham rage was produced we found evidence for inhibition of the pupillary constrictor tonus and for sympathetic excitation, leading to greater dilatation of the normal than of the sympathectomized pupil and to contraction of the nictitating membrane on the normal side. On the other hand, we frequently observed that hypothalamic stimulation which did not cause any typical signs of sympathetic excitation (such as contraction of the nictitating membrane, galvanic response or marked pupillary difference with greater dilatation on the normal side) produced pupillary dilatation of the sympathectomized eye. Such a reaction was often accompanied by a rise in blood pressure. Whether pupillary and blood pressure effects are the results of inhibitory influences on the parasympathetic system or of a combination of parasympathetic inhibition and sympathetic excitation, although the galvanic reflex and the response of the nictitating membrane were absent, cannot be decided at this time. Attention must be called, however, to the important fact that the autonomic responses elicited by stimulation of the forebrain result in various combinations of sympathetic and parasympathetic

excitation and inhibition. Figures 3 and 4 *B* illustrate cases in which thalamic stimulation resulted in a fall in blood pressure together with pupillary dilatation of the normal and of the sympathectomized eye. The fall in blood pressure may be the result either of parasympathetic excitation or of sympathetic inhibition, whereas the pupillary reaction is due to parasympathetic inhibition. Obviously, there are no definite rules determining the mutual relationship between parasympathetic and sympathetic excitation on central stimulation. Similarly, Ranson, Kabat and Magoun [2a] found that hypothalamic stimulation may be accompanied by contraction of the bladder and rise in blood pressure, indicating simultaneous parasympathetic and sympathetic excitation. These conclusions are supported furthermore by new experiments of Gellhorn,[13] who showed that central excitation of autonomic centers by anoxia, metrazol and rage leads at the same time to a sympatheticoadrenal and a vagoinsulin discharge.

Another fact of interest is the presence of pupillary dilatation caused by inhibition of the tone of the third nerve on stimulation of various parts of the thalamus. There was no indication of sympathetic excitation of either the dilator of the pupil or of the nictitating membrane. These results are in agreement with observations of Ury and Gellhorn,[4] who found that pain elicits in normal cats a pupillary dilatation by inhibition of the parasympathetic fibers, although a sympathetic response may be evoked after sensitization of sympathetic centers with metrazol.

In accordance with the results of earlier workers (Karplus and Kreidl[14]) and contrary to the observations of Ranson and his co-workers,[2] we have found moderately large increases in blood pressure on stimulation of the thalamus. This might be accounted for by our use of anesthetics, particularly of chloralosane (a compound of chloral hydrate and dextrose), which leave the animal in a very excitable condition. This suggestion finds special support from our results on blood pressure, which could be widely varied by factors that alter the level of excitation, such as operative shock and the amount and type of anesthetic. In less excitable cats we obtained a decrease in blood pressure on stimulation of the same region that in more excitable cats gave an increase in pressure.

In the case of the changes in sweating resistance or potential, the evidence here obtained agrees with the generally accepted view of the sympathetic innervation of the sweat mechanism. The extreme diffi-

13. Gellhorn, E.: Physiological and Pharmacological Investigations on the Nature of Hypothalamic Excitation, read at the meeting of the American Psychiatric Association, Cincinnati, May 22, 1940.

14. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halsympathikus, Arch. f. d. ges Physiol. **129**:138-144, 1909; II. Ein Sympathikuszentrum im Zwischenhirn, ibid. **135**:401-416, 1910.

culty we have experienced in obtaining galvanic responses from cats under even very mild anesthesia leaves open the question whether the mechanisms here in control of sweating are the only ones operative in the waking animal.

SUMMARY

The excitation of various parts of the forebrain of the cat with faradic currents and the recording of the reaction of the pupil (normal and sympathectomized), the nictitating membrane, the blood pressure and the galvanic reflex have shown that parasympathetic inhibition, as indicated by pupillary dilatation of equal degree in the normal and in the sympathectomized eye, may be obtained from the corona radiata, the basal ganglia and the hypothalamus and pretectal area. In the hypothalamus this response may be associated with signs of sympathetic excitation.

In general it has been found that the intensity of the autonomic response increases as the electrode descends from the corona radiata through the thalamus into the hypothalamus.

From the pretectal region constriction of the pupil is elicited, followed by dilatation (inhibition of parasympathetic control).

Parasympathetic and sympathetic responses may appear in various combinations, indicating that the excitation or inhibition of one branch of the autonomic nervous system does not determine the nature of the excitatory process in the other, functionally opposed division.

Dr. Gerhardt von Bonin advised us as to the histologic technic.

CEREBRAL SWELLING AND EDEMA ASSOCIATED WITH CEREBRAL TUMOR

A HISTOGENETIC AND HISTOPATHOLOGIC STUDY

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With increasing knowledge of cerebral functions the difficulties of localization in cases of tumor of the brain tend to diminish. There remains, however, a large number of cases in which accurate localization and successful operation are hindered by the rapid evolution of the disease. In the majority of such cases cerebral swelling and cerebral edema play an important part; indeed, these two reactions of the brain tissue may be considered as one of the greatest obstacles to the diagnosis and treatment of tumors of the brain. It is perhaps largely on this account that, in spite of advances made in neurosurgery in recent years, the treatment of cerebral tumors is often not as favorable as it should be.

Histopathologic studies of the problems presented by cerebral tumors, among which the investigations of Cushing and Bailey, Hortega, Ostertag, Marburg, Globus and Roussy and Oberling may be mentioned, have added much to understanding of tumor structure, but these studies have been concerned principally with the classification and morphologic character of the tumors and with the dysontogenetic factors which they display. I believe, however, that for a clear understanding of the natural history of a cerebral tumor it is necessary to consider the influence of the tumor on the brain as a whole, and not the morphologic features of the tumor itself and its local destructive effects alone. If this is done, one can more readily understand why in some cases the evolution is rapid and in others slow, for this irregularity of development cannot always be explained by the histologic nature of the tumor. Until recently it was generally thought that only the most malignant tumors run a rapid course; in my opinion, this is not always true. Many instances are known in which a malignant tumor had a relatively slow, chronic course; on the other hand, there are numerous cases in which a benign tumor (e. g., an endothelioma) caused death in the course of several weeks. This seeming irregularity

From the Clinique Neurologique of the Hospice de la Salpêtrière (Prof. G. Guillain).

in the clinical picture, which leads to uncertainty in prognosis, can be explained by a complete study of the whole brain; in the majority of such cases, pathologic reactions (cerebral edema and cerebral swelling) in parts distant from the tumor can be discovered. Recently, I have shown that the acute course in many cases of tumor is dependent on cerebral edema or cerebral swelling.[1]

The term cerebral edema (*Hirnödem*) has long been in use, and the reaction has often been reported in cases of such diverse conditions as cerebral vascular accidents secondary to cardiorenal disease, certain grave intoxications (diphtheria and peritonitis), status epilepticus and even catalepsy. Anton (1904) defined cerebral edema as an increase in the volume of the brain secondary to an increase in the fluid in the perivascular and pericellular spaces. Reichardt [2] was the first to introduce the concept of cerebral swelling (*Hirnschwellung*) as a specific reaction of nerve tissue; he arranged his cases in two etiologic groups: (1) cases in which the reaction was brought about by an exogenous agent, e. g., cerebral tumors, infections and intoxications, and (2) cases in which no exogenous cause could be discovered. Swelling of the brain of endogenous origin he observed in some cases of epilepsy and catatonia. Of recent years many papers have appeared, mostly in the German literature, on the relation between cerebral tumor and cerebral swelling and cerebral edema (Jaburek,[3] Füngeld,[4] Spatz,[5] Stengel [6] and Scheinker). While the greater number of investigators (Reichardt, Redlich, Tagaky) concluded that swelling of the brain is a rare complication of cerebral tumor, Spatz [5] stated that true swelling of the brain is of common occurrence in cases of cerebral tumor and is the direct cause of the increased intracranial pressure. In the majority of recent German publications the opinion has been expressed that a distinction should be drawn between cerebral swelling and cerebral edema (Spatz). It must be added that in the English and American literature the con-

1. Scheinker, I.: Zur Histopathologie des Hirnödems und der Hirnschwellung bei Tumoren des Gehirnes, Deutsche Ztschr. f. Nervenh. **147**:137-162, 1938; Ueber das gleichzeitige Vorkommen von Hirnschwellung und Hirnödem bei einem Falle einer Hypernephrommetastase des Kleinhirnes, ibid. **148**:1-16, 1938.

2. Reichardt, M.: Hirnschwellung, Allg. Ztschr. f. Psychiat. **75**:34-103, 1919.

3. Jaburek, L.: Hirnödem und Hirnschwellung bei Hirngeschwülsten, Arch. f. Psychiat. **104**:518-547, 1936.

4. Fünfgeld, E.: Hirnschwellung und Hirntumor, Deutsche Ztschr. f. Nervenh. **114**:209-213, 1930.

5. Spatz, H.: Die Bedeutung der "symptomatischen Hirnschwellung" für die Hirntumoren und für andere raumbeengende Prozesse in der Schädelgrube, Arch. f. Psychiat. **88**:790-794, 1929.

6. Stengel, E.: Zur Pathologie der letalen Hirnschwellung (Ein Beitrag zur Kasuistik der Fernwirkung von Hirntumoren), Jahrb. f. Psychiat. u. Neurol. **45**:187-200 (Sept. 1) 1927.

cept of cerebral swelling as distinct from cerebral edema does not exist; in fact, cerebral edema is the only term commonly employed. In French articles the two terms appear to have been used indiscriminately, but le Beau [7] concluded that it was impossible any longer to draw a distinction between them. His conclusions, however, were based entirely on a macroscopic study of the brain.

Thus, an important question arises: Is there a characteristic and specific histologic picture of cerebral swelling? That such a picture exists has until now been denied by all authors. In the literature in general it is stated that cerebral swelling is a pathologic reaction of the brain tissue without any histologic changes.

The only histologic abnormality reported was described by Alzheimer,[8] who observed glial proliferation (ameboid change) and degeneration of the macroglia in cases of apparent cerebral swelling. In cases more recently studied, Spatz [5] found glial changes, though these were variable and inconstant. The most constant abnormalities were swelling of the glia fibers and clasmatodendrosis of the macroglia. However, it must be said that such glial reactions are common to a vast number of cerebral lesions and are probably to be regarded as nonspecific. Because of this, Pette,[9] in a critical review of the subject, stated that hitherto all investigations of the problem had proved unsuccessful. More recently, however, I [1] reported the following constant histologic lesions in cases of cerebral swelling: (1) uneven rarefaction and hydration of the ground substance, giving rise to a reticulated appearance; (2) increase in the number of the protoplasmic glia cells, which showed a marked tendency to ameboid degeneration, and (3) functional vascular disturbances (stasis and diapedesis), which I regarded as the probable cause of the other changes.

Physicochemical researches on cerebral swelling reported by de Crinis [10] afford perhaps an explanation of these histologic changes. By means of the xanthydrol method he showed that in cases of swelling of the brain there is considerable retention of urea in the brain tissue. This, in his opinion, increases the osmotic pressure in the brain tissues, with consequent hydration of the albumin. These results were confirmed experimentally by Heim (1938), who showed in addition

7. Le Beau, J.: L'oedème du cerveau, Thesis, Paris, 1938.

8. Alzheimer, A., in Nissl, F.: Beiträge zur Frage nach der Beziehung zwischen klinischem Verlauf und anatomischem Befund bei Nerven- und Geisteskrankheiten, Berlin, Julius Springer, 1914, vol. 1, pt. 2.

9. Pette, H.: Klinik der Hirngeschwülste, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:10-69, 1938.

10. de Crinis, M.: Ueber die Hirnschwellung, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:149-152, 1938.

that retention of urea leads to increased absorption of fluid into the pericellular colloidal envelope. These workers expressed the belief that retention of urea with consequent hydration of the albumin is the fundamental cause of cerebral swelling; if this view is correct, the principal histologic lesions which I have described receive a rational explanation.

Here it may be pointed out that Spatz [5] asserted that the macroscopic picture of cerebral swelling is so typical that the diagnosis should never be in doubt. He stressed the almost total obliteration of the subarachnoid space and the close approximation of the arachnoid and the dura mater. He also pointed out that the subarachnoid space contains hardly any cerebrospinal fluid, that the convolutions are so flattened that their identification is rendered extremely difficult and, finally, that the outer surface of the brain appears unusually dry.

I shall now describe the results of my own investigation, based on histologic examination in 10 cases of cerebral swelling and cerebral edema selected from the rich material of the Hospice de la Salpêtrière. It is not possible to give all the histologic details in more than 1 case of each of the two conditions; observations in the other cases will be incorporated in the general conclusions. I hope to show that the histologic pictures of these two conditions, already described in my first two publications, are sufficiently characteristic for histologic diagnosis and differentiation.

Unfortunately, it is not possible in the present cases to describe fully the macroscopic appearance of the meninges and the surface of the brain, because of the long preservation of the brains in formaldehyde.

REPORT OF CASES

CASE 1.—*History.*—L. L., a man aged 36, in 1919 sustained a doubtful injury to the head, without loss of consciousness. Since 1921 he had complained of intermittent headaches in the left frontal region and brief "lapses," as often as four or five a day, which were always preceded by an ill formed visual hallucination. In the six months before admission to the hospital the headaches became more severe and continuous; his general health declined, and his gait became unsteady. Vision slowly deteriorated, and there was occasional diplopia in looking down. Speech became difficult, and psychic troubles (moria) appeared.

Examination.—Vision was 6/10 in the right eye and 5/10 in the left eye. There were bilateral papilledema, of high grade, and defective convergence of the eyes.

Ventriculograms outlined the right ventricle only.

Operation.—Exploration of the right rolandic area failed to disclose the tumor. After operation left hemiplegia appeared. The patient died one month after the operation.

Autopsy.—The convolutions were greatly flattened. A large meningioma was observed beneath the right temporal lobe, which obviously arose from the lesser

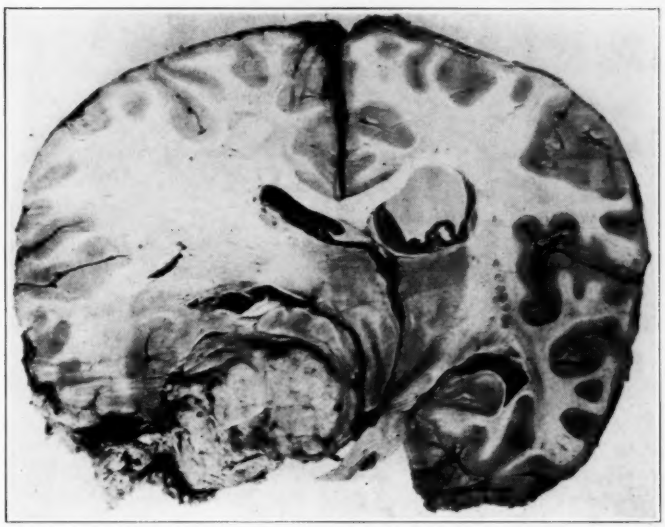

Fig. 1.—Frontal section of the brain in a case of cerebral swelling.

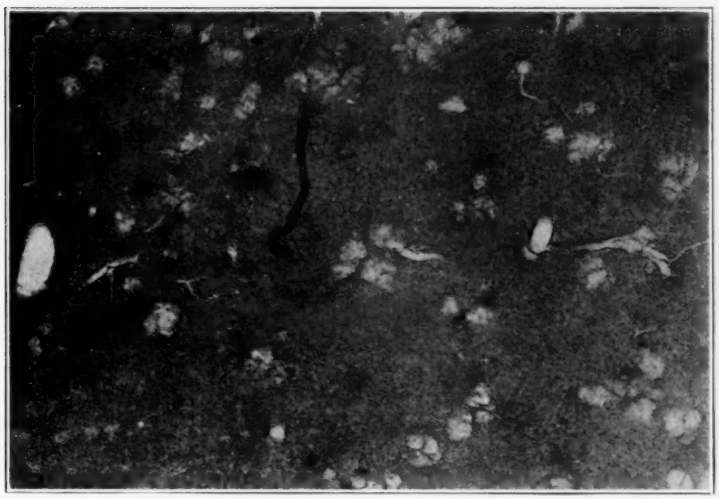

Fig. 2.—Section taken 5 cm. from the margin of a tumor, showing rarefaction of the ground substance in a case of cerebral swelling.

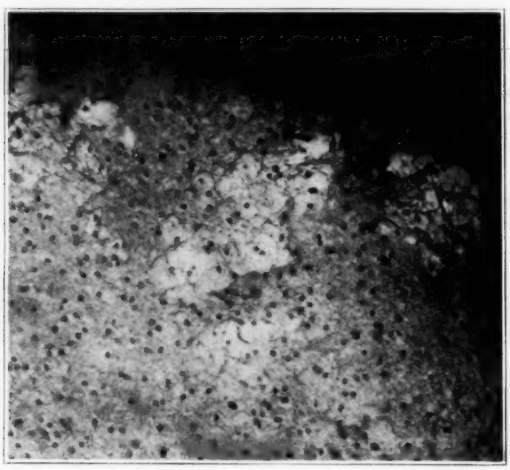

Fig. 3.—Section taken from a region at a distance from a tumor, showing the earliest changes in cerebral swelling.

Fig. 4.—Bielschowsky preparation of the white matter at a distance from the tumor, showing changes in the axons associated with cerebral swelling.

wing of the sphenoid bone. Figure 1 shows a frontal section bisecting the tumor, which indicates the greatly increased bulk of the hemisphere. The increased volume was due solely to the increased width of the white matter. The lateral ventricle was almost obliterated, and the septum lucidum and the third ventricle were displaced to the right. The tumor was sharply delimited from the cerebral tissue, except laterally.

Histologic Examination.—In the substance of the hemisphere about 5 cm. from the margin of the tumor the ground substance showed early rarefaction and reticulation (fig. 2). Close inspection revealed swelling of all the constituent tissues (axons, myelin sheaths and glia). Furthermore, there was slight glial proliferation.

In this case it was possible to follow the pathologic processes more fully in areas in which the lesions were minimal. Figure 3 is a low power view of a region far removed from the tumor; here the earliest changes of cerebral swelling

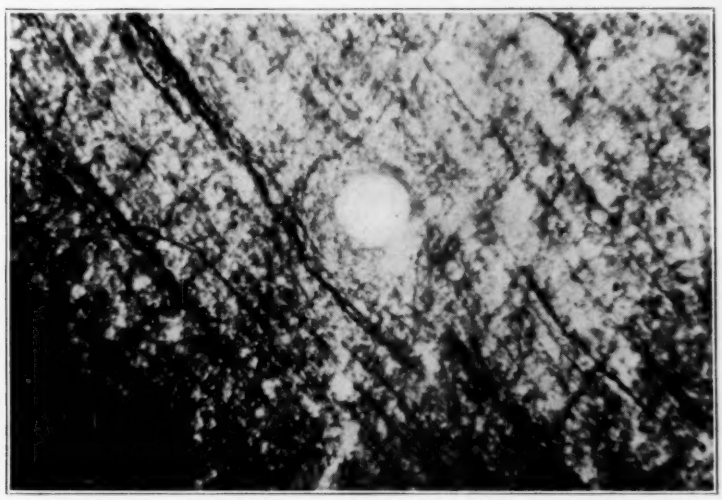

Fig. 5.—Section near the margin of the tumor, showing severe changes in the myelin sheaths in a case of cerebral swelling.

can be seen. There were small discrete foci of rarefaction in the midst of otherwise normal white matter. Examination of these foci with higher magnification showed that they were the result of reticulation of the ground substance. The glia cells had taken on the protoplasmic form, and the cytoplasm was seen as a distinct halo around the nucleus. Examination of Bielschowsky and Spielmeyer preparations showed edematous swelling of the axons and myelin sheaths (fig. 4), with consequent but irregular alteration of the normal picture. Enclosed in the "mesh" in the foci of rarefaction were occasional gitter cells and (rarely) gemästete cells containing altered blood pigment.

The vascular changes were noteworthy. In the foci of rarefaction it was common to see greatly dilated capillaries and arterioles. Accompanying this hyperemia was exudation of plasma into the perivascular spaces. Often erythrocytes were seen in the perivascular spaces (diapedesis), together with local accumulations of leukocytes within the vessels. It may be presumed that these

definite vascular changes represent the morphologic equivalent of the functional vascular disturbances described by Ricker [11] and Schwartz.[12]

In preparations nearer the edge of the tumor the lesions were much more severe. The small foci of rarefaction had become confluent, and the swelling of the cells and processes was more severe and widespread. The entire white substance was extremely pale, and only occasionally were there small strands of relatively well preserved myelin (fig. 5). On the whole the axons were much less affected, but here and there irregular swelling and "torpedo bodies" were seen. The progressive and regressive changes in the glia were more advanced. In many of the protoplasmic astrocytes the nucleus was pyknotic and shrunken, with homogenization of the cytoplasm; in short, the condition approached the ameboid state. Parallel with this all stages of clasmatodendrosis were observed.

In general, analysis of the histologic changes which I have observed in cases of cerebral swelling permits the following conclusion: There is slight alteration of the nerve tissue characterized by rarefaction and hydration of the ground substance; hydration with swelling of the myelin sheaths, axis-cylinders and glia cells, and, in addition, mild functional vascular disturbances (stasis and diapedesis).

I shall now describe a typical case of cerebral edema.

Case 2.—*History.*—P. H., a man aged 49, who was admitted to the Hospice de la Salpêtrière on Nov. 10, 1927, had presented the initial symptoms of the illness about the end of July 1927, in the form of insidious deterioration of speech and inability to recall the appropriate word, followed by misplacement of words. In August he began to complain of generalized headache. In October weakness of the right arm appeared and the headache became continuous. On admission to the hospital he was drowsy and aphasic. He died on Nov. 17, 1927.

Autopsy.—The entire left hemisphere was abnormally large. The consistence and degree of dryness of the cut surface were not ascertained. A horizontal section (fig. 6) showed that the swelling was limited to the white matter. A poorly delimited, greenish yellow area, situated in the left occipitotemporal region proved to be a glioma.

Histologic Examination.—There were two principal types of abnormalities: (1) vascular lesions and (2) lesions in the nerve tissue proper.

1. Vascular Changes: These lesions were most important, and will be described first. With a low power lens generalized passive hyperemia was visible. The majority of the capillaries were distended with blood, and the signs of stasis and damming of the circulation could be seen almost everywhere. The lumens of the capillaries and small arterioles were abnormally increased. These circulatory changes were much more striking in the white substance, in which the majority of the small vessels were enlarged and surrounded by a large homogeneous area of transudate. In some places this transudate had led to general liquefaction of the surrounding nerve tissue. These changes could all be explained as a result

11. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180-212, 1919.

12. Schwartz, P.: Die Arten der Schlaganfälle des Gehirns und ihre Entstehung, Berlin, Julius Springer, 1930.

of vascular stasis of some duration, which had led to a lesion of the vessel walls, resulting in increased permeability and thus transudation of serous fluid.

In the deeper parts of the cortex a certain degree of vasodilatation and perivascular distention was present, but it was much less intense than in the white matter. Here and there a small vessel was surrounded by a clear zone, more often by a deposit of amorphous material which was faintly reticulated and stained rose with the Van Gieson method. This amorphous material was probably fibrin in the transudate from the adjacent vessel. Rarely a small perivascular hemorrhage was seen. More frequent were small accumulations in the perivascular spaces of glia cells which contained altered blood pigment. Sometimes compound

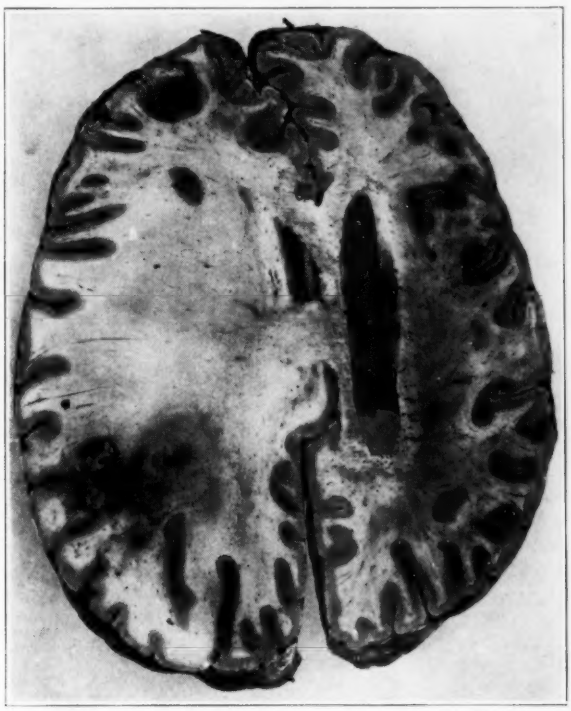

Fig. 6.—Horizontal section of the brain in a case of cerebral edema.

granular corpuscles were seen. The tissue immediately adjacent to these vessels had a ragged or "threadbare" appearance.

2. Lesions in the Nerve Tissue Proper: In the white matter, about 5 cm. from the edge of the tumor, characteristic perivascular lesions were visible even in low power views. They took the form of areas of pallor, but the ground substance presented an alveolar or sievelike appearance (fig. 7). The interstices of this reticulum appeared vesiculated, and many of the vesicles contained nuclear debris. Glia cells were numerous and frequently showed vacuolation and swelling of the cytoplasm. These glial changes recalled the acute swelling of the oligodendroglia which Penfield observed in a variety of pathologic states. Such changes were confined almost entirely to the immediate vicinity of the vessels;

despite their intensity, it was the rarefaction and fenestration of the ground substance which appeared to be the more important and suggestive lesion. In Spielmeyer preparations the myelin was severely affected. The white matter was everywhere abnormally pale, and around many of the smaller vessels had entirely disappeared. On the other hand, the myelin in the immediate subcortical region was better preserved and in the cortex appeared normal. Bielschowsky preparations showed that the axons were irregularly swollen and poorly impregnated, particularly in the vicinity of vessels.

The pericellular spaces, as described by Obersteiner, which are not normally visible, were here apparent. They varied but always were most marked in the deeper parts of the cortex and sometimes had a concentrically laminar form. They recalled the lesions noted by Alajouanine in cases of arterial encephalopathy and by Lhermitte in cases of air embolism.

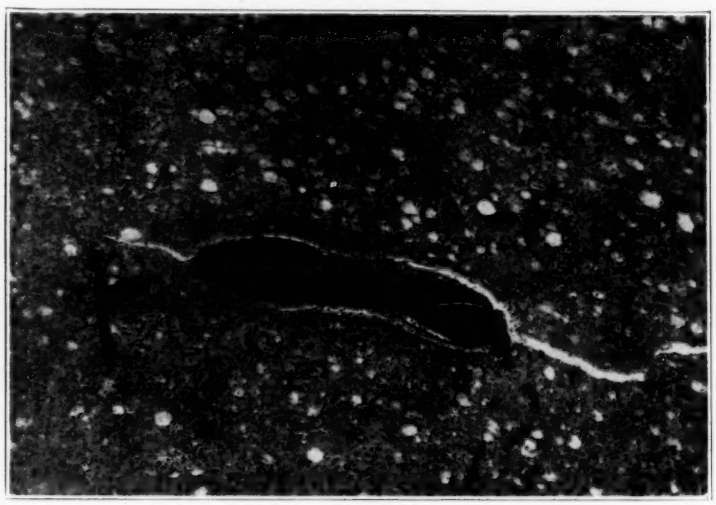

Fig. 7.—Section of nerve tissue 5 cm. from the margin of a tumor, showing the sievelike appearance of the white matter in a case of cerebral edema.

The cortical ganglion cells, as seen in Nissl preparations, were pale and showed a variable degree of chromatolysis. A more severe, but less common, change was pyknosis of the nucleus, with diffuse staining of the cytoplasm and slight swelling of the processes (the ischemic cell of Spielmeyer).

Such is the typical histologic picture of cerebral edema. Analogous changes were observed in all the other cases examined. Briefly, the picture can be summarized as follows: (1) morphologic signs of alteration of the circulatory system, with an increase in the permeability of the vessel walls; (2) distention of the perivascular spaces; (3) transudation of serous fluid into the nerve tissue around the blood vessels, with resulting liquefaction of the tissue; (4) distention of the pericellular spaces, and (5) an areolar and sievelike appearance of the nerve tissue.

These observations demonstrate the typical picture of cerebral edema and show how important a role is played by vascular disturbances in its genesis. This opinion is fully in harmony with the results of Alajouanine, who several times in recent years has described exactly similar vascular changes and concluded that they were of fundamental importance.

Jakobi and Magnus produced experimental cerebral edema by ligation of cerebral vessels; in this connection the observations and conclusions of Vincent [13] are of interest. He noted on several occasions the sudden onset of swelling of the frontal lobes during the course of an operation. In his second case, also one of suprasellar meningioma, a small hemorrhage was accompanied almost immediately by swelling of the frontal lobe. With respect to both cases he remarked:

> There was swelling of the lobes, due apparently to vascular engorgement and edematous infiltration, comparable with those of urticaria.

It may be added that in 5 similar cases 2 patients recovered and 3 died.

Similar acute swelling was also noted by Vincent in a case of cerebellar tumor at the moment when the vascular pedicle of the tumor was cut. In this case the patient suffered from considerable arterial hypertension.

The observations recently published by Alajouanine and Hornet [14] in cases of "generalized cerebral edema" are of interest in this connection. They concluded:

> Microscopic examination revealed, above all, vascular alterations consisting of intense vasodilatation with stasis involving veins and arteries and attacking the smallest vessels, together with distention of the perivascular sheath with edematous and even blood-containing fluid.

The true origin of these circulatory disturbances has not yet been ascertained; on the basis of the present observations, one may suggest only the possibility of a functional vascular disturbance. This opinion is perhaps strengthened by the operative experiences of Vincent, which have already been mentioned.

Le Beau suggested that at least two centers exist the activity of which may, under certain circumstances, give rise to acute cerebral edema: one in the hypothalamus and the other in the medulla oblongata.

This hypothesis has little evidence for its support; for the present at any rate, it seems wiser to relate these episodes of acute edema to a disturbance of general vegetative or vital function. In this way one

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13. Vincent, C.: Les fonctions du lobe frontal vues par un neurochirurgien, Rev. neurol. **64**:544-546 (Oct.) 1935.

14. Alajouanine, T., and Hornet, T.: L'oedème cérébral généralisé (étude anatomique), Ann. d'anat. path. **16**:133-163 (Feb.) 1939.

may understand certain puzzling, but well known, phenomena which may occur in cases of cerebral tumors, such as the sudden change in the clinical picture resulting from a relatively trivial cause (slight trauma, mild infection, the ventriculographic procedure). In such circumstances cerebral edema or cerebral swelling is almost always the lethal factor, and its onset is such that sudden vasomotor paralysis seems the most likely cause. In this connection it may be recalled that Pette [9] laid emphasis on the great lability of the entire vascular system in many cases of intracranial tumor.

It may be added that some authors (Struwe [15] and Hoff and Urban [16]) have postulated localized vascular stasis around the tumor, which by extension leads to generalized cerebral edema. Jaburek opposed this hypothesis and drew attention to the perivascular infiltration as indicating a toxic-inflammatory origin of cerebral edema. I, too, have found such a round cell perivascular infiltration in some cases, but it seems more prudent to regard this as a simple reactive phenomenon, such as is known to occur in many cerebral disease processes.

CONCLUSIONS

This study is based on a histologic examination of 10 cases of cerebral swelling and cerebral edema. I have shown that these two conditions can be considered as fairly distinct pathologic syndromes.

In cases of cerebral edema I have described the typical and well known picture of the areolar, sievelike appearance of the nerve tissue and distention of the pericellular and perivascular spaces, with resulting liquefaction of the nerve tissue. However, I have drawn particular attention to the morphologic signs of alteration of the circulatory system with increase in the permeability of the vessel walls.

In cases of cerebral swelling such morphologic changes in the vessels are absent. In this condition these are mild functional vascular disturbances only (stasis and diapedesis), and usually the capillaries alone are involved. The alterations of the nerve tissue are not marked, and consist particularly of hydration and rarefaction of the ground substance, with hydration and swelling of the axis-cylinders, myelin sheaths and glia cells.

In cerebral edema the presence of an increase of tissue fluid in the interstitial spaces may be easily inferred. In cerebral swelling, on the other hand, the process is, rather, physicochemical hydration of the entire protoplasm, with consequent swelling of the individual cells.

15. Struwe, F.: Beitrag zur Klärung der Hirnschwellungsfrage aus dem klinischen Verlauf und dem makroskopischen und mikroskopischen Hirnbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:503-520, 1931.

16. Hoff, H., and Urban, H.: Zur Frage des Ödems bei Hirngeschwülsten, Deutsche med. Wchnschr. **60**:1537-1541 (Oct. 12) 1934.

It is to this fact that the difference in the histologic pictures of cerebral swelling and cerebral edema is to be attributed. This physicochemical hydration is apparent histologically only when it has attained a certain degree of intensity. This may explain the absence of findings reported by many workers.

The relatively slight lesions observed in cases of cerebral swelling indicate the possibility of a reversible process, while the severe lesions seen in cerebral edema seem irreversible.

Despite the histologic difference between cerebral swelling and cerebral edema, I believe that, fundamentally, the two conditions are only two stages of the same biologic process. The problem is to state where the one begins and the other ends.

The fundamental cause of cerebral swelling and cerebral edema remains unknown. Both are the expression of a basically similar reaction of the cerebral tissues to a variety of noxious stimuli and seem to depend on a generalized vasomotor disturbance.

Prof. G. Guillain placed his cases at my disposal, and Dr. Ivan Bertrand gave helpful advice and made available facilities for this investigation.

MESCALINE HALLUCINATIONS IN ARTISTS

W. S. MACLAY, M.D., M.R.C.P.
AND
E. GUTTMANN, M.D., L.R.C.P. (EDIN.)
LONDON, ENGLAND

The various theories about the cause of hallucinations have been largely influenced by the material which the writers studied. Thus, Mayer-Gross formed his theory on observation of the fantom limb, Schroeder on observation of delirious states and Vogt on experience with electrical stimulation of the cerebral cortex. It lies in the nature of the subject that its study is based mainly on verbal descriptions, given by patients with more or less impaired ability to describe their experiences. It was realization of this drawback which made so attractive the study of hallucinations experimentally produced in normal subjects by drugs such as mescaline. Work by Mayer-Gross, Stein, Zucker and others has proved the fruitfulness of this study of "experimental psychosis."

Mescaline hallucinations are predominantly, though not exclusively, visual, so that a description of them by means of drawings and pictures could be expected to be somewhat more impressive, and perhaps more realistic, than a verbal account, which may be adequate for hallucinations of the auditory type but is liable to contain certain fallacies in describing experiences of the visual type.

As described in a previous paper,[1] patients' drawings were used in studying schizophrenic symptoms of the visual type; but with patients the scope of the procedure is limited not only by their impaired mentality but also by their ability or inability to draw. In an experimental study on normal persons, however, the subjects can be chosen with care, as was done in this investigation, in which it was possible to find artists who were willing to volunteer their services. They were given enough mescaline to cause hallucinations and were asked to sketch what they saw and then after the intoxication was over to make another drawing of their experience in retrospect.

This study was made with the support of the Rockefeller Foundation.

From the Mill Hill Emergency Hospital, Dr. W. S. Maclay, medical officer in charge.

1. Guttmann, E., and Maclay, W. S.: Clinical Observations on Schizophrenic Drawings, Brit. J. M. Psychol. **16**:184, 1937.

It is surprising to find so few illustrations of mescaline hallucination in the numerous publications on the subject. Two facts may account for this: one, the general laziness and inactivity which are produced by the drug; the other, the fleeting and ever changing character of the visions.

Some of the drawings obtained during these experiments are shown in this paper. They will illustrate what can be explained, if not proved, as being due to physiologic factors effective in the production of these hallucinations, at the same time allowing for and giving full value to the nonphysiologic (psychologic) factors at work. The fact that the subjects were artists not intimately known to the authors precluded any attempt to analyze in detail the content of the drawings.

According to Klüver,[2] mescaline visions are characteristically of three types: (*a*) tapestry, grating, lattice, fretwork, filigree, honeycomb or chessboard design; (*b*) tunnel, funnel, alley, cone or vessel patterns, and (*c*) spirals.

It is on the constancy of these phenomena that Marshall [3] based his conclusion that there must be a peripheral stimulus producing them. This theory is applicable in some cases but needs elaboration in others.

OBSERVATIONS

Figure 1 is the best example of the tapestry pattern in the collection; it was evolved by the subject from a hazy drawing made during the first hour of the experimental intoxication. Marshall has collected sufficient evidence to show that, under suitable experimental conditions, the choroid capillaries can be observed normally. Their appearance closely resembles the picture painted by our subject. Moreover, since the same pattern has been obtained from other subjects, it seems justifiable to assume that it was the choroid that was perceived and painted. In addition to the physiologic factors which Marshall used to explain the phenomena, it must be emphasized that with mescaline intoxication the after-images are particularly clear and impressive, even if the stimuli have been feeble (Mayer-Gross and Stein [4]), and that they may persist for abnormally long periods and may be projected on any background. This may explain how the artist was able to reproduce an image that may have existed only momentarily.

The origin of the design in figure 2 is probably similar. Without much imagination it can be interpreted as a picture of the eyeground with the retinal artery and its branches. It again is a normal phenomenon, becoming apparent under the influence of the drug. Apart from the physiologic factors described by Marshall and the intensification of imagery, increased introspection may play a part in the production

2. Klüver, H.: Mescal: The "Divine" Plant and Its Psychological Effects, London, Kegan Paul, Trench, Trubner & Co., 1928.

3. Marshall, C. R.: An Enquiry into the Causes of Mescal Vision, J. Neurol. & Psychopath. **17**:289, 1937.

4. Mayer-Gross, W., and Stein, O.: Psychopathologie und Klinik der Trugwahrnehmungen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1928, vol. 1, pp. 427-507.

of this vision, but it is not proposed to discuss in this paper to what extent the instructions given and the experimental situation led the subjects to observe their experiences more carefully or how far the direction of attention toward visual experiences is an integral part of mescaline intoxication.

Figure 3 (original in color) illustrates photopsia and closely resembles colored scotomas, which Marshall was inclined to explain as peripheral phenomena. This

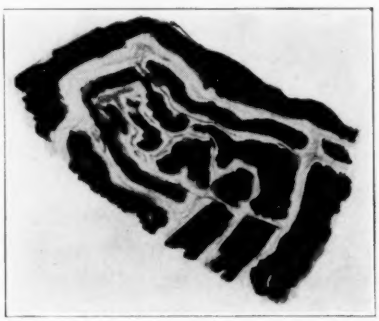

Fig. 1.—Tapestry pattern observed during mescaline intoxication.

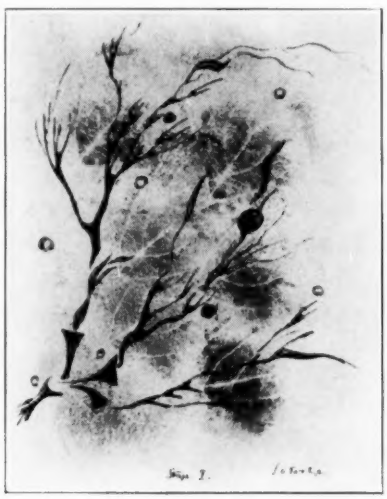

Fig. 2.—Pattern resembling the eyeground, with retinal artery and its branches, observed during mescaline intoxication.

view is difficult to prove or disprove; phenomena like them are described both after peripheral stimulation, such as a blow or pressure on the eyeball, and after central stimulation, such as electrical stimulation of the exposed cortex. Experiences in other intoxications, such as chronic alcoholism and delirium tremens, show that a central alteration lowers the threshold for peripheral stimuli (this is generally assumed as the explanation of the fact that pressure on the eyeball causes photopsia easily in persons with alcoholism). A gradual transition between pho-

topsia, illusion and hallucination has been observed in persons with mescaline intoxication by Mayer-Gross and Stein, who emphasized the theoretic importance of this observation. In connection with the present paper, it points at least to a central component in the causation of phenomena as illustrated here.

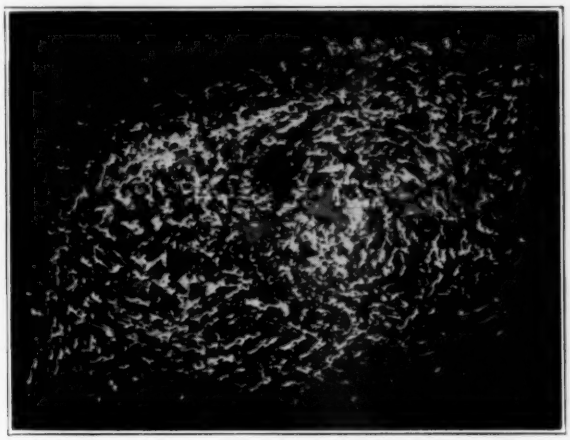

Fig. 3.—Photopsia during mescaline intoxication.

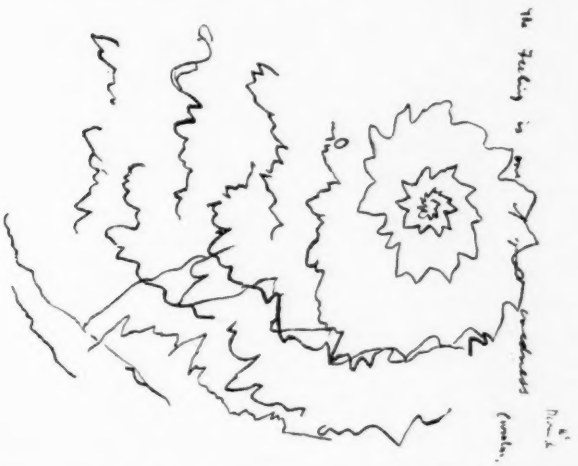

Fig. 4.—Spreading of zigzag lines (colored in original) seen during mescaline intoxication.

The spreading of colored zigzag lines, as illustrated in figure 4, is similar to that described by some patients with migraine, though the hemianopic distribution is not obvious, the flickering is firmer and the angles are less clear than in the usual fortification patterns. The zigzag lines, as illustrated, are seen by the artist as moving from the center to the periphery, but to the observer it is clear that there is only a short step from these phenomena to the repetitive patterns which have been described so often by persons with mescaline intoxication.

Engerth, Hoff and Pötzl [5] were able to demonstrate in cases of disease of the brain how repetitive simple photomas gradually develop into hallucinations of definite shape and content. The picture which shows these phenomena has already been reproduced in a previous paper.[6] A number of primitive repetitive scribbles found in the mescaline series resembled spontaneous drawings, usually known as "doodles," and cannot be interpreted with certainty as pictures of hallucinatory phenomena, but in a few the elaboration is clearly visible which changes elementary visual sensations into hallucinations. The artist who drew the castle and the houses (fig. 5 *A*) explained that he had seen them, though their shape and position changed persistently, but he also pointed out later that the style was similar to that of his previous paintings. Still more striking is the elaboration in the drawings of another subject, who did them during the period of actual intoxi-

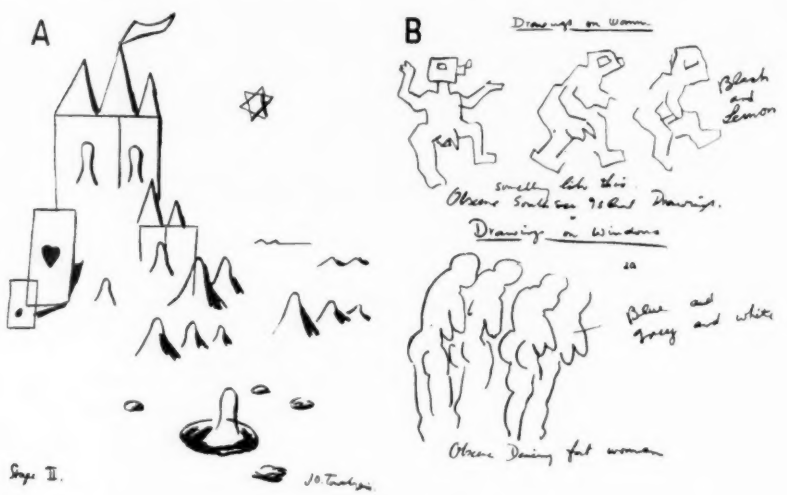

Fig. 5.—Examples of elaborate hallucinatory phenomena.

cation (fig. 5 *B*). Their particular content could be accounted for by the artist in psychologic—in fact psychoanalytic—terms, but the repetitive character can only be explained physiologically.

A few experiments carried out with these artists and a small number of other subjects demonstrated this tendency to repetition. The subjects were given four or five meaningless patterns, taken from Cattell's group tests, to copy and were asked to reproduce them from memory immediately afterward. This test was repeated, different patterns being used at various stages of the intoxication. Any mistakes that were made showed this repetitive character. Figure 6 demonstrates this in 3 of 4 instances.

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5. Engerth, G.; Hoff, H., and Pötzl, O.: Zur Patho-Physiologie der hemianopischen Halluzinationen, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:399, 1935.

6. Maclay, W. S.; Guttmann, E., and Mayer-Gross, W.: Spontaneous Drawings as an Approach to Some Problems of Psychopathology, Proc. Roy. Soc. Med. **31**:1337, 1938.

Figure 7 illustrates another interesting phenomenon of mescaline intoxication. The artist observed that everything he hallucinated seemed to elongate itself in whatever direction he turned his attention. When he tried to draw the man's arm, it grew longer and longer and continued into the cathedral which he held in his hand. The cathedral continued into the spire, the spire into the cross and its ends into airplanes, which are given in an inset to the left of the main figure. The horizontal beams of the cross also show this tendency to elongation. It is interesting to

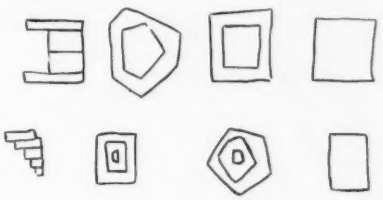

Fig. 6.—Demonstration of repetitive character of phenomena during mescaline intoxication.

Fig. 7.—Phenomenon of mescaline intoxication illustrating elongation of point of interest.

see how the cathedral appears again on the head of the man, though it is not elaborated there. The artist stopped drawing because he was overwhelmed by the way in which the shapes continued indefinitely.

Again, it seems the only possible explanation that the comprehensible contents and their logical connection are superimposed on the physiologic phenomenon which interferes with the definition of visual perception. Many subjects describe how "everything fluctuates," and there are several drawings illustrating wavelike

movement in the visual perception. Figure 8 is interesting in that it was drawn the morning after the experiment and still shows the prevalence of wavy lines. These are entirely foreign to the artist's ordinary style but were marked in his sketches made during the intoxication, so that there can be little doubt about their causation by the drug. The wavelike structure in these sketches is also the best example of distortion of vision that our collection, incomplete in this respect, can offer.

Fig. 8.—Picture made the morning after the experiment, showing the prevalence of wavy lines, an effect of the mescaline.

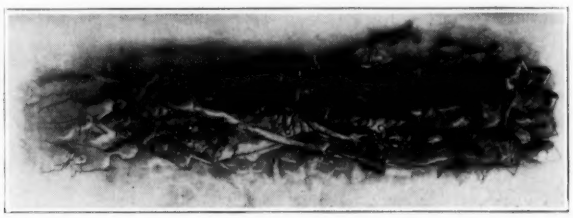

Fig. 9.—Illustration of the complexity of the phenomena during mescaline intoxication.

Figure 9 is the best illustration of the complexity of the phenomena; the artist tried to convey the impression of appearing and disappearing visions; he demonstrated the pareidolic type of illusion, seeing in the gray background shapes and figures of varying degrees of definition. When questioned, the artist said that he saw these pictures without active effort on his part; he did not change them, but they disappeared or changed their appearance when he tried to concentrate on them. He would have been unable to draw them during the intoxication, and it was only with difficulty that he could give this retrospective account in drawing.

COMMENT

These observations provide material for discussion of the two opposing views concerning the origin of hallucinations: the physiologic theories, by which they are regarded as the result of irritation of sensory centers or pathways, and the psychologic, by which they are regarded as projected mental images assuming an external sensory appearance when presented to consciousness.

All the pictures presented show features well known in the physiologic process of seeing or in pathologic conditions due to organic lesions of the visual apparatus. The first few pictures can be accounted for entirely in physiologic terms; in the later ones there are more and more features, the last picture almost representing the free play of fantasy.

In other words, the hallucinations during mescaline intoxication cannot be explained in either physiologic or psychologic terms alone. The fact of hallucinating and some formal characters of the hallucinations are so similar to physiologic and pathologic phenomena that they can be assumed to be physiologic in origin, but psychologic experiences determine the contents of the hallucination; for example, it can be said that the appearance and repetition of similar shapes are caused physiologically, but the facts that the subject sees women and not men and that the scotomas take on the shape of lotus flowers can be accounted for only in psychologic terms.

These observations on mescaline intoxication cannot be applied to other conditions without further study. In other hallucinatory states the relative importance of physiologic and psychologic factors may be different; the former may be more important in patients with gross cerebral irritation, the latter in patients in a hysterical twilight state. Further investigation is necessary to determine the factors which are responsible for their relative importance.

CONNECTIONS OF THE MEDIAL GENICULATE BODY IN THE CAT

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It has been reported [1] that after complete decortication in the dog auditory acuity is appreciably impaired but acoustic function is by no means obliterated. Furthermore, such an animal can be differentially conditioned to pure tone (1,000 cycles) and complex sound (electric bell). The inference is that acoustic integration of a fairly high degree may occur in the absence of the cerebral cortex, that is, may be mediated by entirely subcortical mechanisms.

It has apparently been assumed that the residual acoustic function in the decorticate dog is mediated at the thalamic level, which can only mean the medial geniculate body through its efferent connections. The implication is that the medial geniculate body is not only a relay center in the central auditory pathway but an important reflex center as well. It is difficult to reconcile this conception with the fact that the medial geniculate body (pars dorsalis) very largely degenerates when the temporal cortex is extirpated (Papez,[2] Walker [3] and others). At the same time, it becomes necessary to know in detail what fibers, in addition to the acoustic radiation, emanate from the nucleus. The presence of such fibers, if they exist, should be demonstrated by Marchi studies following lesions of the medial geniculate body.

The Marchi studies of Poliak [4] and of Woollard and Harpman [5] have demonstrated the general plan of cortical projection of the medial

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Communication 38 from the Laboratory of Physiological Psychology (Animal Hearing), which was transferred from the University of Illinois to the University of Rochester in 1938. This laboratory is maintained with aid from the Research Council, American Otological Society.

1. Mettler, F. A.; Mettler, C. C., and Culler, E.: Effects of Total Removal of the Cerebral Cortex, Arch. Neurol. & Psychiat. **34**:1238-1249 (Dec.) 1935.

2. Papez, J. W.: Thalamic Connections in a Hemidecorticate Dog, J. Comp. Neurol. **69**:103-120, 1938.

3. Walker, A. E.: The Retrograde Cell Degeneration in the Thalamus of Macacus Rhesus Following Hemidecortication, J. Comp. Neurol. **62**:407-419, 1935.

4. Poliak, S.: Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Univ. California Publ. Anat. **2**:1-363, 1932.

5. Woollard, H. H., and Harpman, A.: The Cortical Projection of the Medial Geniculate Body, J. Neurol. & Psychiat. **2**:35-44, 1939.

geniculate body in the monkey and the cat, respectively. In a recent communication Bremer and Dow [6] have shown by an oscillographic technic the probable area of primary acoustic projection in the cortex of the cat. The problem of the exact termination of the geniculotemporal radiation has long been subject to the greatest confusion, chiefly because of differences and inadequacies of technic. Two excellent reviews of the pertinent literature are to be found in the aforementioned papers of Woollard and Harpman and Bremer and Dow, and need not be repeated here.

The present communication includes reports on Marchi studies on the cat following lesions of the medial geniculate body, as well as additional oscillographic evidence concerning the functional limits of the primary projection area of the acoustic system.

METHOD

Electrolytic lesions were made in the medial geniculate body by aid of a stereotaxic instrument, the electrode being inserted vertically through a small drill hole in the skull cap. Animals were killed after postoperative periods of ten to twenty days. The brains were then treated by the Marchi method and sectioned at 50 microns (pyroxylin). Fifteen cats were used.

Cortical response to sharp mechanical clicks delivered 1 foot (30 cm.) from the cat's ear was measured by means of a single phase, capacity-coupled amplifier recording on a cathode ray oscillograph. The active electrode consisted of a thread moistened in saline solution, drawn through a hypodermic needle and anchored to the skull by a holder so constructed as to permit movement in any direction; the animal was grounded by means of a clip lead attached to adjacent skin or muscle. The electrode, in light contact with the pia mater, was moved systematically in 2 mm. steps over an area sufficiently large to permit exact definition of the boundaries of the responsive cortex.

RESULTS

Exclusive of the geniculotemporal radiation, two principal types of pathways emanate from the medial geniculate body. The first consists of diffuse connections to other parts of the diencephalon and midbrain. It must not be supposed that these fibers form a well defined geniculothalamic tract, such as Rioch [7] (page 349) described from an examination of normal material. Rather, the fibers are few, widely scattered and obscure as to precise termination. Some apparently enter the central gray matter surrounding the anterior portion of the aqueduct; others, having left the hilus of the medial geniculate body in a medial and anterior direction, appear to terminate in or near the midline nuclei of

6. Bremer, F., and Dow, R. S.: The Acoustic Area of the Cerebral Cortex in the Cat: A Combined Oscillographic and Cytoarchitectonic Study, J. Neurophysiol. **2**:308-318, 1939.

7. Rioch, D. McK.: Studies on the Diencephalon of Carnivora: III. Certain Myelinated-Fiber Connections of the Diencephalon of the Dog (Canis Familiaris), (Felis Domestica), and Aevisa (Crossarchus Obscurus), J. Comp. Neurol. **53**: 319-388, 1931.

the same side, especially the nucleus reuniens. In several of the animals, degenerated fibers could be seen to enter the posterior commissure, cross and turn ventrally, circling downward just lateral to the central gray matter.

Degenerated fibers were seen in nearly all the animals to enter the deep portion of the superior colliculus. It is considered doubtful, however, whether these constitute a genuine geniculocollicular tract. The electrode was in all cases inserted vertically, which means that some visual fibers were necessarily severed by the electrode where they lie dorsal to the medial geniculate body. Woollard and Harpman failed to note any such fibers in their preparations when they inserted the electrode from behind (horizontally), thus avoiding all retinotectal fibers.

The most notable and consistent group of subcortical connections consists of recurrent fibers passing to lower acoustic centers. In all cases, a definite group of fibers in the brachium of the inferior colliculus degenerated. These were not numerous as compared with the total number of fibers in the brachium and tended to be scattered throughout rather than to occupy a particular region of the tract. They were of relatively fine caliber and could be seen to enter the inferior colliculus.

A well marked, though again diffuse and comparatively minor, component of the lateral lemniscus degenerated after lesions of the medial geniculate body. It is impossible to say precisely where these fibers terminate. It can be stated with assurance, however, that in at least 5 of the animals degenerated fibers could be traced into the trapezoid body itself, possibly to terminate on the cells of that region.

It is interesting to note that the recurrent fibers of the lower acoustic pathway have their counterpart in the fibers projecting from the temporal cortex to the medial geniculate body (Mettler [8]). It might be said, then, that the principle of reverse innervation between cortex and thalamus postulated by Papez [9] holds for the entire acoustic system. A mechanism is thus provided whereby higher centers, having received impulses from lower ones, may in turn affect the activity of these lower centers.

In the absence of strong connections from the medial geniculate body to any motor mechanism, and in view of the fact that the medial geniculate body degenerates after temporal lobectomy, it is difficult to consider this nucleus as an important reflex center for audition, capable of functioning independently of the temporal cortex. So far as present knowledge goes, however, the lower portions of the acoustic pathway can function to some extent even after the geniculotemporal complex has been destroyed. There are probably numerous connections from the inferior colliculus as well as from the primary nuclei to motor centers of the brain stem. The precise nature of these remains to be elucidated.

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8. Mettler, F. A.: Connections of the Auditory Cortex of the Cat, J. Comp. Neurol. **55**:139-183, 1932.

9. Papez, J. W.: Personal communication to the author.

It has long been thought that the commissure of Gudden provides an interconnection of the two medial geniculate bodies. Rioch [7] indicated that part of the medial root of the optic tract (the so-called tract of Gudden) arises from the pars ventralis of the medial geniculate body. Woollard and Harpman, on the other hand, observed no degeneration of the commissure after any of their lesions of the medial geniculate body, at least some of which, they asserted, must have involved cells of the pars ventralis. Such degeneration was observed in only 2 of the 15 animals used in the present study. In both cases the lesion was situated at the lateral extremity of the nucleus, overlapping into the medial portion of the adjacent optic tract. In no animal in which the lesion was confined within the borders of the medial geniculate body was any degeneration of Gudden's commissure found. This can only mean that in the 2 animals degeneration of the commissure was due to direct involvement of the fibers of Gudden's tract, and that the medial geniculate body contributes no fibers to the tract and commissure. Thus, the commissure of Gudden is in no sense a "geniculate commissure." The bilateral cortical representation of each organ of Corti, clearly demonstrated by Brogden and his co-workers,[10] must depend on crossing of acoustic fibers at a level below the medial geniculate body, presumably in the trapezoid body alone.

With regard to the geniculotemporal radiation, the present degeneration experiments can contribute little additional information to that presented by Woollard and Harpman (fig. 1 *A*). With the exception of the inferior boundary of the projection area, our results agree with theirs. That is, the medial geniculate body projects on an area bounded anteriorly by the anterior ectosylvian sulcus, posteriorly by the posterior ectosylvian sulcus and superiorly by the suprasylvian sulcus. Inferiorly, the agreement fails. Woollard and Harpman indicated termination of geniculotemporal fibers nearly down to the rhinal fissure. The present experiments, on the contrary, point to the superior end of the pseudosylvian sulcus as the absolute inferior limit. This agrees with the oscillographic findings reported on later in this paper. It may also be pointed out that the area so bounded corresponds closely with that which in primates forms the upper surface of the superior temporal gyrus, whereas the sylvian cortex itself, included in Woollard and Harpman's projection area, in primates is folded inward to form insula.

The experiments of Bremer and Dow indicated a more limited area of cortical projection than that determined by Woollard and Harpman. Whereas Woollard and Harpman included nearly the whole sylvian gyrus, Bremer and Dow reported only the area stippled in figure 1 *B*

10. Brogden, W. J.; Girden, E.; Mettler, F. A., and Culler, E.: Acoustic Value of the Several Components of the Auditory System in Cats, Am. J. Physiol. **116**:252-261, 1936.

as responsive to acoustic stimulation. It will be seen also that there is a minor discrepancy between their electrical and cytoarchitectonic maps (fig. 1 *B* and *C*).

In the present experiments it was found that sharp mechanical clicks delivered 1 foot from the ear of a cat under anesthesia (pentobarbital sodium) produced correlated potential responses in the cortical area indicated by stippling in figure 2 *A*, *B*, *C* and *D*. The response assumed the form of a relatively slow spike followed, and sometimes preceded,

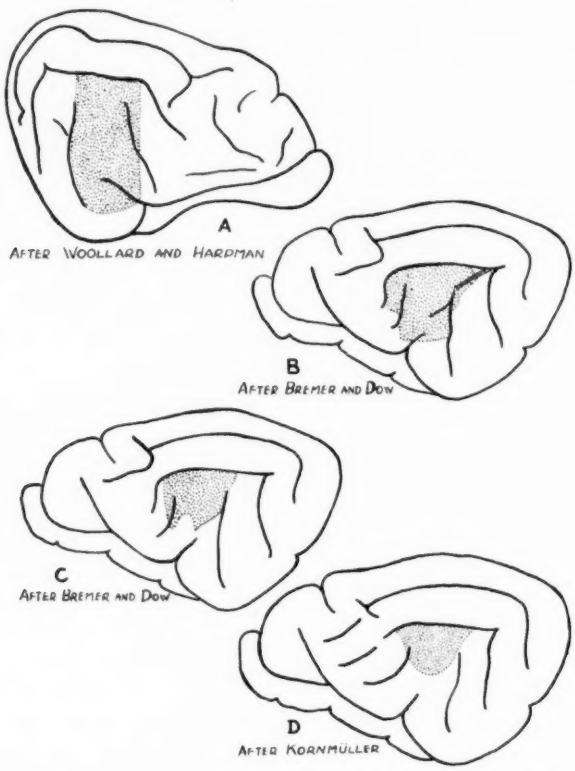

Fig. 1.—*A*, area of termination of the geniculotemporal radiation as shown by Woollard and Harpman [5] (cat). *B*, area responsive to click stimulation according to Bremer and Dow [6] (cat). *C*, cytoarchitectonic map of the primary acoustic cortex according to Bremer and Dow [6] (cat). D, combined cytoarchitectonic and functional maps of the primary acoustic area according to Kornmüller [11] (cat).

by potentials of opposite phase, slower speed and much lower amplitude. There was a certain variability within the responsive area, both in magnitude of response and in relative size of the positive and negative components. However, beyond the area indicated in the figures the magnitude of response dropped abruptly to zero, compared with which

change the internal variations were negligible. Of particular significance is the fact that the projection area as defined by this means had the same borders under deep and light anesthesia. This was determined by tests at different levels of anesthesia on the same cats.

Figure 2 *A*, *B*, *C* and *D*, each representing the primary projection area defined in a separate experiment (different animals), show that the area is confined to the most superior extremity of the sylvian gyrus and the middle ectosylvian gyrus. It is obviously subject to considerable variation of extent in different animals. If the areas stippled in the four figures are superimposed on a single drawing (fig. 2 *E*), it can be

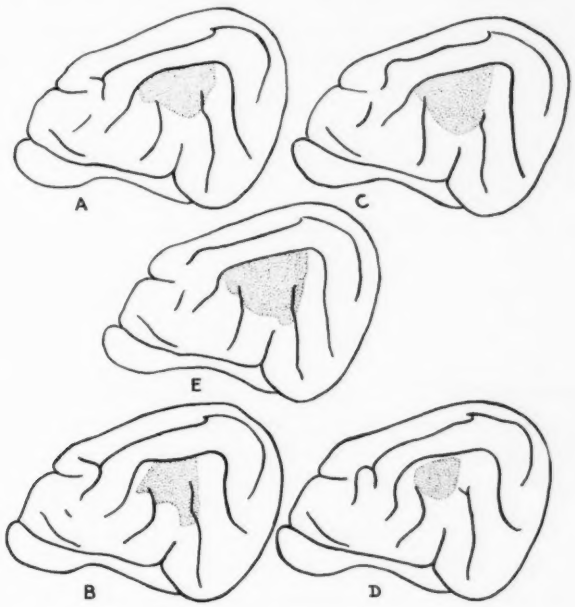

Fig. 2.—*A*, *B*, *C* and *D*, primary acoustic areas of 4 cats as determined by cortical electrical response to click stimulation. *E*, combined maps of the same 4 cats plotted on a single drawing.

seen that the total area involved corresponds closely with the cytoarchitectonic map of Bremer and Dow (fig. 1 *C*), but falls short of their electrical map both anteriorly and inferiorly. These results, then, seem to coincide closely with the cytoarchitectonic area outlined by Bremer and Dow and the electrical and cytoarchitectonic map of Kornmüller [11] (fig. 1 *D*).

11. Kornmüller, A. E.: Bioelektrische Erscheinungen architectonischer Felder: Eine Methode der Lokalisation auf der Grosshirnrinde, Deutsche Ztschr. f. Nervenh. **130**:44-60, 1933.

From comparison of *A, B, C* and *D* of figure 2, it will be seen that considerable variation exists in the functional acoustic areas of different cats even when tested under exactly the same conditions. It may be safely assumed, therefore, that the agreement of these results with those of Bremer and Dow and of Kornmüller is as good as can be expected. Since each cat has a different pattern, which can be determined only by individual examination, it seems clear that nothing is to be gained by increasing further the number of animals tested.

SUMMARY

1. Recurrent fibers pass from the medial geniculate body to the inferior colliculus and to the trapezoid body by way of the brachium of the inferior colliculus and the lateral lemniscus, respectively, and thus provide a system of reverse innervation between subcortical acoustic nuclei.

2. Diffuse fibers leave the medial border of the medial geniculate body and pass to other parts of the thalamus and midbrain.

3. No evidence is found to support the contention that the medial geniculate body has any important function as an acoustic reflex center.

4. The commissure of Gudden does not connect the two medial geniculate bodies.

5. Fibers pass from the medial geniculate body to a cortical area bounded anteriorly by the anterior ectosylvian sulcus, posteriorly by the posterior ectosylvian sulcus, superiorly by the suprasylvian sulcus and inferiorly by the superior extremity of the pseudosylvian sulcus. This area coincides with that responsive to acoustic stimulation.

Case Reports

RHYTHMIC MYOCLONUS

A Clinical Report of Six Cases

JOHN P. DOBSON, M.D., AND HENRY ALSOP RILEY, M.D., NEW YORK

Rhythmic myoclonus may be described as a regularly recurrent muscular contraction, without opposing movements of antagonistic muscles. It is to be distinguished from nystagmus, in which slow motion of one muscle group is followed by a quick rectifying motion of an opposing muscle group, and from tremor, in which antagonistic groups of muscles contract irregularly and in opposite directions. It also differs from both of these and from all other myoclonic movements in its nearly perfect rhythmicity and its persistence during sleep. It can temporarily be suspended by voluntary contraction of the affected muscles.

It is observed most frequently in muscles of the oropharynx but is also found in muscles of the face and eyes, the larynx, the diaphragm and the intercostal muscles and more rarely in the muscles of the upper extremities.

Correlation of this clinical manifestation with definite pathologic alterations was established by Guillain, Mollaret and Bertrand,[1] who outlined a triangular area in the brain stem lying between the inferior olive, the red nucleus and the contralateral dentate nucleus. These nuclei and the pathways between them, chiefly the central tegmental tract, were consistently found to be involved in patients presenting this rhythmic myoclonic disturbance.

For a more detailed analysis and a review of the literature reference may be made to articles by Guillain, Mollaret and Bertrand [1] and Riley and Brock [2] and to a report of the pathologic observations in a case studied clinically by Davison, Riley and Brock.[3]

We shall describe the clinical findings in 6 cases in which this interesting phenomenon was manifested—4 from the neurologic service of the First Division, Welfare Hospital, 1 from the West Service of the Neurological Institute of New York, and 1 that of a private patient.

From the Department of Neurology, Columbia University College of Physicians and Surgeons; the Neurological Service of the First Division, Welfare Hospital, and the Neurological Institute of New York.

1. Guillain, G.; Mollaret, P., and Bertrand, I.: Sur la lésion responsable du syndrome myoclonique du tronc cérébral, Rev. neurol. **2**:666, 1933.

2. Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Pharynx, Larynx and Other Regions: Clinical Report of Three Cases, Arch. Neurol. & Psychiat. **29**:726 (April) 1933.

3. Davison, C.; Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Larynx and Other Regions, Bull. Neurol. Inst. New York **5**:94, 1936.

REPORT OF CASES

CASE 1.—*History.*—F. D., a white man aged 65, had had transient episodes of weakness on the left side five years before admission to the hospital. The attacks were usually brought on by overindulgence in alcohol and disappeared when the influence of alcohol wore off. After about a year of this course of events he was afflicted one morning with a sudden shooting pain in the left side of his head, followed by weakness of the left side, vomiting and unconsciousness, of about a day's duration. There then developed double vision, deafness and dizziness. The dizziness disappeared in two months, but the left hemiparesis, diplopia and deafness have persisted to the time of writing.

The past history revealed frequent alcoholic bouts, and it was said that he had had a positive Wassermann reaction of the blood fifteen years before, for which he received no treatment. He had always been excitable and prone to violent emotional reactions to minor stimuli.

Physical Examination.—The temperature, pulse and respiration were normal. The blood pressure was 185 systolic and 115 diastolic. Vision in the left eye was markedly reduced as a result of a corneal opacity. Both eyes showed rhythmic, counterclockwise movements at a constant rate of 80 per minute. The pupils were small and equal and reacted promptly to light. Paresis of the right exteral rectus muscle was present. Conjugate movement of the left eye with the right eye was absent. Attempts at fixation forward produced a left internal squint. Rhythmic myoclonus, synchronous with the movements of the eyes, was present at the right corner of the mouth and on the left side of the neck. The same type of movement was observed in the muscles of the pharynx and palate, the motion being predominantly toward the left at a rate of 80 contractions per minute and synchronous with the movements of the eyes and face. Laryngeal examination by Dr. Page Northington revealed myoclonic movements in both vocal cords, the movement being greater in the left cord; the direction of the quick component was toward the midline. The myoclonic movements disappeared on voluntary innervation of the larynx. There was weakness of the left side of the face of central type. An audiometer test showed impairment of hearing in the right ear as compared with the left. Caloric tests were difficult to evaluate because of the rhythmic myoclonus of the eyeballs.

The left extremities were paretic and spastic, with slow asynergia accompanying intention movements. The reflexes were exaggerated in the right upper extremity but could not be elicited in the right lower extremity because of the extreme spasticity. No definite Babinski sign could be obtained.

Sensory examination showed diminution of joint position and vibratory sense, especially in the left lower extremity. Pain and temperature sensibilities were markedly reduced in the left upper extremity and, to a generally lesser and variable extent, over the rest of the left side; this was less evident in the face, where there was loss of moderate degree, only in the distribution of the mandibular nerve.

Laboratory Data.—The urine, the blood count and the results of chemical examination of the blood were essentially normal. The Wassermann reactions of the blood and spinal fluid were negative.

CASE 2.—*History.*—T. L., a white woman aged 58, ten months before admission had suddenly experienced an attack of vomiting, without nausea, followed by weakness of the left side. No loss of consciousness took place. During the following two weeks there developed speech difficulties, diplopia, dizziness and involuntary

nodding movements of the head. The diplopia disappeared, but the other disturbances have persisted, with little or no improvement, to the present time.

Mild diabetes, for which she received treatment by diet, had existed during the three years prior to the present illness.

Physical Examination.—The temperature, pulse and respiration were normal. The blood pressure was 98 systolic and 76 diastolic. Irregular nodding motions of the head were observed. There was weakness of lateral movement of the right eye. Disorganization of conjugate movements of the eyes was produced by a tendency to internal squint of both eyes. The pupils reacted equally to light and in accommodation. There was loss of sense of pain and temperature on the left side of the face. Weakness of the left lower part of the face was noted. A rhythmic twitching was present in the left side of the neck, and rhythmic contractions of the left side of the palate and pharynx occurred at the rate of 148 per minute. Examination by Dr. Page Northington revealed slight movements about the opening of the eustachian tube on the right side. The myoclonic movement was seen in the arytenoid cartilages and the vocal cords, the quick component being toward the midline. The amplitude of the movement was greater on the right side. Hypesthesia of the pharynx and the larynx was discovered. The left arm and leg were weak. The right arm and leg were ataxic and presented fair muscular power; occasional choreiform movements of the right hand were observed.

The tendon reflexes of the right extremities were more active than those of the left. The ankle jerk was absent on both sides. The plantar response on the left side differed from that on the right, but was not definitely abnormal. The abdominal reflexes were absent bilaterally.

There was marked loss of sense of pain and temperature over the left side of the body and the face. Tactile, vibratory and joint position sensibilities were normal throughout.

Laboratory Data.—The Wassermann reactions of the blood and spinal fluid were negative; the colloidal gold curve was normal. Urinalysis on admission showed the presence of a moderate amount of sugar, which disappeared after a few weeks during which the patient received an appropriate diet, without insulin.

CASE 3.—*History.*—S. B., a man aged 65, a Turk, was admitted to the medical service because of cough and fever. Aphonia and lack of contact with members of his family prevented the obtaining of an adequate history, but a friend stated that about a year previously the patient had suddenly lost consciousness and fallen. A short period of unconsciousness was followed by marked difficulty in speech. The patient was admitted to Bellevue Hospital, where he suffered another vascular accident, which resulted in complete loss of the ability to speak. On rare occasions he could emit sounds. Great difficulty with deglutition also developed. After admission to the Welfare Hospital the cough and fever disappeared in about a week, but the aphonia and dysphagia remained.

Physical Examination.—The temperature, pulse and respiration were normal. The blood pressure was 170 systolic and 120 diastolic. The patient was unable to speak and swallowed with difficulty. The pupils were equal and reacted to light. There was some difficulty in upward gaze and in convergence of the eyeballs. There were moderate impairment of the jaw movements and moderate paresis of the right lower portion of the face. Hearing was apparently normal, as judged by response to commands. In all other tests requiring spoken answers accurate information could not be obtained.

The soft palate showed rhythmic myoclonic movements at the rate of 130 per minute, the contractions being more marked on the left side. The pharyngeal reflex was absent. The gait was slow and somewhat spastic in the right lower extremity. There was no material loss of power in any of the limbs. The deep reflexes were generally overactive, particularly in the right extremities. The Babinski reaction was variably present in the right foot. The Rossolimo reaction was positive in both feet. Sensory perceptions were difficult to evaluate because of the aphonia, but seemed at least roughly normal.

Laboratory Data.—The Wassermann reactions of the blood and spinal fluid were negative. The colloidal gold curve was normal.

CASE. 4.—*History.*—B. P., a man aged 81, a German, was unable to give a history because of an advanced degree of mental deterioration. No adequate history was obtained. He was admitted to the Welfare Hospital with paralysis of the right side of extreme degree and moderate paresis of the left side.

Physical Examination.—The temperature, pulse and respiration were normal. The blood pressure was 170 systolic and 110 diastolic. The patient was semistuporous, bedridden and incontinent. He rarely replied to questions and then slowly, with only a word or two.

Cataracts were present in both eyes. The left pupil was larger than the right and reacted less briskly to light. The movements of the eyeballs seemed to be normal, although this and other responses requiring cooperation were difficult to elicit.

The tongue protruded in the midline; the left nasolabial fold was less marked than the right. Rhythmic myoclonus of the palate and pharynx, at a rate of 88 contractions per minute, was present.

The patient could move his right arm and leg to a limited extent only. The range of motion in the left arm and leg was somewhat more extensive, but there was marked paresis of both left extremities. All the tendon reflexes were overactive. The abdominal reflexes were absent, and the Babinski reaction was elicited bilaterally.

It was impossible to test sensory perceptions because of the mental status.

Laboratory Data.—The Wassermann reactions of the blood and spinal fluid were negative.

CASE 5.—*History.*—J. J. F., an Irish laborer aged 59, who was first seen in May 1935, gave a history of sudden right hemiplegia occurring on July 27, 1931, followed on the same day by unconsciousness. Speech was much disturbed. Moderate improvement followed, and he became able to walk unaided and to use his right arm to a limited extent. Skilled acts were much interfered with. The improvement continued until February 1933, when for no apparent reason the patient became gradually weaker, more inactive and drowsy. Progressive diminution in speech took place. No real change in the situation developed after May 1933. Examination during the interval indicated additional involvement of the brain stem, producing paralysis of the left side of the face.

Examination.—The patient appeared senile. The blood pressure was 170 systolic and 120 diastolic. The residuals of right hemiplegia were present. Constant rhythmic twitching of the muscles of the posterior pharyngeal wall and soft palate and of the muscles of the neck below the angles of the jaws and about the corners of the mouth was observed. The rate of twitching was about 60 contractions per minute. It was continuous except for interruptions produced by voluntary innervation. There was reduction in strength in all limbs, more marked on the right

side. Some incoordination was present in both lower extremities. Only hoarse, guttural, entirely unintelligible noises could be produced. The patient understood simple commands and could recognize objects and indicate their use.

Abnormal plantar reflexes were present bilaterally. It was impossible to determine sensory perceptions on account of poor cooperation. The retinal arteries were moderately arteriosclerotic; the pupils were slightly irregular and reacted restrictedly to light; bilateral lenticular opacity was present. The pharyngeal and palatal reflexes were present.

The patient was overactive emotionally and presented some confusion.

Laboratory Data.—The blood count was normal, and the Wassermann reaction of the blood was negative; the results of chemical examination of the blood were normal. Examination of the spinal fluid revealed a 1 plus reaction for globulin and 63 mg. of protein per hundred cubic centimeters, and the Wassermann reaction, with both crude and cholesterolized antigens, was 1 plus with 0.2 cc., 2 plus with 1 cc. and 4 plus with 2 cc.; no evidence of block was present.

CASE 6.—*History.*—J. W. C., a white man aged 65, was first seen in December 1923. The diagnosis of a psychoneurosis, anxiety state, was made. At that time physical and laboratory examinations gave normal results. The patient was seen again in 1933, at which time the systolic blood pressure was 200 mm. of mercury. The hypochondriacal anxiety state had continued. In December 1934 he suffered mild right hemiparesis after a severe dizzy spell with nausea. His speech became thick, and double vision developed.

Examination.—The patient presented right conjugate deviation and gross incoordination and awkwardness of the right upper and lower extremities, interference with skilled acts of the right hand and groping athetoid movements. The reflexes were relatively unchanged. There was diminution of all types of sensation, particularly deep sensibilities in the right arm, hand and leg. Diplopia was present on attempts to look to the left, and there was absence of conjugate movement to the left. The blood pressure was 150 systolic and 100 diastolic.

Course.—At the time of the examination the diagnosis of a left pontile tegmental vascular accident was made, the lesion involving the levo-oculogyric mechanism, with evident vestibular disturbance and involvement of the mesial fillet.

This subsequently improved to a considerable extent but never returned entirely to normal. A feeling of unreality and deadness in the right hand persisted; difficulty in equilibration continued, and huskiness of the voice gradually developed.

In July 1936 rhythmic myoclonus of the pharyngeal wall was observed. No similar movements were found elsewhere.

The patient died of coronary occlusion in May 1937. Necropsy was not performed.

COMMENT

This series of cases adds nothing new to the already well established clinical picture of rhythmic myoclonus. All the patients were relatively advanced in years; all but 1 showed definite arterial hypertension and evidences of extensive arteriosclerosis, both general and cerebral. All patients presented evidence of involvement of the brain stem, principally disturbances in the control of ocular movements, loss of conjugate gaze, weakness of one or the other external rectus muscle, facial palsy or bilateral involvement of the larynx. Some disturbance in superficial or deep sensibilities was determined in all the patients who were capable of sufficient cooperation to supply adequate informa-

tion. Either one or both pyramidal tracts had been involved, as indicated by the history or determined by clinical examination. Only 1 patient presented a positive Wassermann reaction of the spinal fluid. The distribution of the rhythmic myoclonic movements differed in each case, except in 2 in which the characteristic movement was shown only in the posterior pharyngeal wall. In all cases the involuntary movement was inhibited by voluntary innervation.

This series is reported merely to place these cases on record and to indicate that in any service with patients suffering from chronic neurologic disorders it is probable that similar cases may be discovered if the functional territories of the cerebral nerves, from the oculomotor to the vagus, are carefully examined.

Dr. Maurice Frocht took painstaking care in making a beautiful cinematographic recording in these cases.

JUVENILE HUNTINGTON'S CHOREA

EUGENE I. FALSTEIN, M.D., AND THEODORE T. STONE, M.D., PH.D., CHICAGO

In 1872, when Huntington[1] published his famous account of "hereditary chorea," which later led to the naming of the disease for him, he stressed three essential characteristics, namely, the hereditary nature, the tendency to insanity and suicide and the age at which the onset occurs. His emphasis on the need to live to adult age in order that symptoms of the affliction may develop led for many years to the general conviction that an onset of symptoms in the third to the fifth decade of life is almost pathognomonic of Huntington's chorea; even today many neuropsychiatric texts define the disease in these terms.

Prior to 1904 most of the published papers dealing with Huntington's chorea were concerned with clinical and pathologic descriptions of the disease. In 1916, Magnus[2] described 2 cases of Huntington's chorea in a man and woman in the thirties. Thereafter, much of the literature became increasingly concerned with the social and eugenic problems offered by the affliction, but few well defined and typical cases occurring in the first two decades of life have been reported.

In her comprehensive monograph on Huntington's chorea, which appeared in 1934, Bell[3] analyzed and summed up all the case histories that had appeared in the literature until that time. In one series of 460 cases, the age of onset of symptoms was listed as under 4 years in 4 instances, between 5 and 9 years in 5 instances, between 10 and 14 years in 15 instances and between 15 and 19 years in 24 instances. Thus, in 48 of 460 cases, or in about 10 per cent, the disease is said to have begun under the age of 20. Bell expressed the suspicion that some of the observations in cases at both extremes of the scale may be of doubtful value and that nervous, or even imitative, movements in a child may have been construed as signs of the disease by apprehensive parents. According to Bell, members of choreic families who have observed the development of the disease frequently detect symptoms when a medical man could not detect their existence; on the other hand, there are those who, consciously or unconsciously, refuse to recognize the presence of symptoms until they are of a disabling character.

We have studied all the cases of the disease among patients admitted to the Elgin State Hospital over a period of thirty-seven years, and have also surveyed all the cases in the Illinois state hospitals as of

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Read by title at the meeting of the Illinois State Medical Society, Peoria, Ill., May 22, 1940.

From the Institute for Juvenile Research, Northwestern University, Department of Nervous and Mental Diseases, and the Elgin State Hospital, Elgin, Ill.

1. Huntington, G.: M. & S. Reporter, Philadelphia **26**:317 (April) 1872.

2. Magnus, W.: Norsk mag. f. lægevidensk. **77**:1133 (Nov.) 1916.

3. Bell, J.: Huntington's Chorea, in The Treasury of Human Inheritance, London, Cambridge University Press, 1934, vol. 4, pt. 1.

Jan. 1, 1937.[4] Our study of the 55 cases at the Elgin State Hospital and their genealogic histories, as well as the available cases in the other hospitals, indicates that there have been only 2 cases of Huntington's chorea in which the disease could with certainty be said to have started under the age of 17.

REPORT OF CASES

CASE 1.—G. K., a 21 year old white girl, was admitted to the Elgin State Hospital on Sept. 7, 1935. Her father is Polish and is living and well. Her mother was of German-Irish extraction.

The family history revealed that the patient's mother, grandmother, great-grandmother and great-great-grandmother died of Huntington's chorea. Her great-grandfather had chronic alcoholism, was in the penitentiary for a time and had delirium tremens on many occasions; he died at the age of 70. His wife's choreiform movements began in the early thirties, and their onset was followed in about two years by definite mental deterioration. She died in a state hospital at the age of 41.

The disease developed in the patient's grandmother at the age of about 30, but the course was more rapid. She was admitted to the Peoria State Hospital in 1910, at the age of 36, and died there two years later. She was the mother of 6 children, 4 of whom were described as degenerate or feebleminded, requiring institutional care. Two sons, maternal great-uncles of the patient, suffered from chronic alcoholism and chorea, both of them receiving care at the Peoria State Hospital on several occasions. They married, but nothing is known of their children. The patient's mother was illegitimate. She was married in 1910; after her third child was born her husband began to notice signs of the same illness from which his mother-in-law had suffered. On Feb. 7, 1920, when 31 years of age, she was admitted to the Lincoln State School and Colony with her youngest daughter, a baby at that time. The latter was sent to an orphanage and the mother was transferred to the Peoria State Hospital on March 6, 1920. She was admitted to the Kankakee State Hospital on July 27, 1920, and died in 1928. Mental symptoms had been noted for five years prior to her admission to the institution at Lincoln and were fully developed at the time she was committed. She had already had 6 children, including, at the time of our patient's commitment, a daughter of 26, a son of 23, whose whereabouts were unknown, a son of 21, the patient, a son of 18 and a daughter of 15. Several maternal cousins are said to be feebleminded. The patient's brothers and sisters are said to be normal at the present time.

The patient became "nervous" about four years prior to her commitment, when she was 16 or 17 years of age. She acted strangely, was irresponsible and displayed temper tantrums. She tried to work as a maid for a time in 1934, but left after a month because of her inability to adjust in her employer's home. She dropped dishes and could not perform fine tasks. Finally, when she had committed several sexual indiscretions and did not appear to realize the significance of what she had done, her father brought her to the Cook County Psychopathic Hospital.

The earlier history revealed little of importance. The patient is said to have completed grammar school. She had smallpox as a child and underwent a mastoid operation at the Cook County Hospital at the age of 14.

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4. Falstein, E. I., and Stone, T. T.: Illinois M. J. **75**:164 (Feb.) 1939.

The physical and neurologic examinations at Elgin State Hospital revealed mild but typical incoordinated, purposeless, jerky movements of the upper and lower extremities, increased deep reflexes, adiadokokinesis, frequent grimacing and a peculiar, hesitant dysarthria. It was noted that when she attempted to sit she stood in front of the chair for about a second, then made a movement to sit down, arrested herself momentarily, appeared to sit on air and then finally seated herself rather clumsily. There were no abnormal general physical findings.

The results of laboratory examination, including urinalysis, serologic tests of the blood, blood count, and determinations of the calcium, phosphorus, cholesterol, sugar, nonprotein nitrogen, creatinine and chlorides of the blood, were normal; examination of the spinal fluid, the van den Bergh test, dextrose and insulin tolerance tests, phosphorus partition tests and determinations of the icteric index, the blood sedimentation rate and the Walter permeability quotient all gave results within normal limits. In this case, the only one of 15 cases of Huntington's chorea studied extensively from the laboratory standpoint in which there was sufficient cooperation for determination of oxygen consumption, the rate was —6.[5]

Mental examination revealed considerable childishness, a moderate degree of euphoria, occasionally associated with irritability and tantrum reactions, and fair to rather poor responses to the usual intellectual tests. The patient was well oriented, presented a few vague ideas of reference and spoke naively of her fairly recent sexual experiences, shamefacedly calling herself a bad girl because she had performed fellatio at the request of several young men and had masturbated frequently since she had experienced heterosexual relations.

A Babcock deterioration scale gave an index of minus 4.8 and a vocabulary intelligence quotient of 88. She cooperated well and appeared to be pathologically deteriorated from a former low average level of intellectual ability. During the two years following her admission, she masturbated openly and manifested occasional periods of excitement, temper tantrums, combativeness and exhibitionistic trends. She was sociably inclined and at times volunteered descriptions of peculiar psychosomatic delusions. The choreiform movements gradually became greater in intensity and extent.

A relatively recent check-up showed that her condition had regressed, and she was found to be markedly deteriorated, incontinent, demented and withdrawn. The choreic movements are very pronounced, and the patient is confined with the most deteriorated hebephrenic patients in the hospital.

CASE 2.—T. C., a 16 year old white girl of German-Irish descent, was seen in the department of admission of the Institute for Juvenile Research in January 1938, having been referred because the school was unwilling to keep her any longer. In addition, she was unmanageable in the home, experienced violent temper tantrums, refused to take care of her clothing and appearance and was jealous of and quarrelsome with her sister, two years younger.

The family history is interesting. The paternal great-grandfather was admitted to the Jacksonville State Hospital, and died there of Huntington's chorea. The paternal grandfather also died of the same disease in the same hospital in 1918, after two admissions to the hospital, the last in 1909. The patient's father was admitted to Jacksonville State Hospital in 1929, after a preceding admission to Alton State Hospital in the same year. Attention had been called to the beginning choreiform movements four years before, when he was 32. A year later he was overcome by the heat while working in the fields. The typical generalized

5. Falstein, E. I., and Stone, T. T.: Illinois M. J. **77**:47 (Jan.) 1940.

choreiform movements had been well established at the time of his admission to the hospital at Jacksonville. He remained there only three weeks and was readmitted in 1931, dying a month later of exhaustion incidental to the violent choreiform movements. A paternal aunt was also admitted to the Jacksonville State Hospital in 1937, suffering from the same disease. She was 35 at the time, and the movements had first been noted at the age of 25. Two living paternal uncles were also afflicted, though they had not been hospitalized, and a paternal great-aunt and her son had been institutionalized at Jacksonville, because of the same disease.

The early history of the patient was essentially without significance. At 9 she suffered from a serious attack of diphtheria; after her recovery she appeared to have changed in that she was more sensitive and asocial, exhibiting more frequent tantrum reactions.

At the age of 14 the patient was referred to a reliable medical clinic because of "nervousness" and backwardness in school. A diagnosis of high grade mental deficiency was made at the age of 15, after an intelligence quotient of 60 had been obtained on a Stanford-Binet test. At that time it was noted that she exhibited peculiar blinking movements. She cooperated well, however, and was fairly attentive.

At the time of her examination at the institute, in 1938, when she was 16, an intelligence quotient of 51 was obtained on a revised Stanford-Binet test. The results of the test, as evaluated by the psychologist, appeared to indicate definite deterioration. Neurologic examination disclosed a rigid, awkward, rather ataxic gait. The deep reflexes were somewhat exaggerated. There was suggestive pseudoptosis of the left upper tarsus, with irregular, spasmodic blinking movements. The patient was unable to perform fine movements in a coordinated fashion, and displayed occasional massive jerking movements of the trunk, especially on the left side. There were occasional twitchings of the arms and legs and grimaces about the mouth.

The psychiatric examination disclosed a peculiar, physically mature, emotionally immature child, who giggled a great deal, was silly in her manner and displayed considerable interest in heterosexual matters. There was evidence of marked jealousy of and rivalry with the younger sister, and she expressed many strongly colored sexual fantasies.

The patient was reexamined three months later, when she was returned because of the mother's inability to supervise her closely, and because she had become involved in several heterosexual affairs.

The choreiform movements appeared to be more prominent at this time, and because of the more serious social and psychiatric implications, the patient was transferred to the Cook County Psychopathic Hospital, where commitment proceedings were initiated.

After a stay of a year at the Chicago State Hospital, where a diagnosis of Huntington's chorea, encephalitis and mental deficiency was made, the girl was paroled to her mother, who sent her downstate to live with her grandmother. There she was careless, neglectful of her appearance, irritable and concerned with childish and regressive pursuits.

COMMENT

It has been puzzling to find only the 2 cases here reported after a detailed investigation of most of the cases in the Illinois state hospitals, whereas Bell has collected a comparatively large series. In a personal

communication to us, Bell [6] stated that cases of Huntington's chorea with an early onset are extremely rare. In her genetic studies, she found that the correlation of ages of onset in members of the same family is very high, so that, to quote her, "one of those rare gametes with an early liability is likely to provide such individual cases. If it is true that the cases in America have sprung mostly from one family, which came from England, one could expect, of course, to find much less variability in the age of onset than in any series of cases from all over Europe."

It is likely, as has already been pointed out, that the European figures have been exaggerated, and it is just as likely that we have failed to obtain accurate descriptions of the onset of the disease in some of our cases. Both of the cases reported appear to be exceedingly interesting and rare, and they tend to show that "anticipation," in which the disease appears at an earlier age in each generation, plays a role in at least some cases of the disease. Our genealogic studies, which have already been published, tend to show, as have many others, that anticipation is, unfortunately, the exception to the rule in this disease.[7]

SUMMARY

Two cases of juvenile Huntington's chorea in which the onset of symptoms could be traced to the late adolescent period of development are presented. These are the only cases of the disease with onset under 20 years of age that we have been able to find in an extensive study of cases in the Illinois state hospitals, particularly the Elgin State Hospital.

43 East Ohio Street.

30 North Michigan Avenue.

6. Bell, J.: Personal communication to the authors.

7. Stone, T. T., and Falstein, E. I.: J. Nerv. & Ment. Dis. **89**:795 (June) 1939.

CLINICAL AND ELECTROENCEPHALOGRAPHIC CHANGES IN A CHILD DURING RECOVERY FROM ENCEPHALITIS

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To our knowledge, no reports have appeared in the literature describing changes in the electroencephalogram over a period following infectious processes which seriously affect the central nervous system. This report presents the clinical and electroencephalographic findings in a child during the course of recovery from an attack of encephalitis.

The illness developed during the period in August and September 1938 in which an epidemic of equine encephalitis appeared among horses and human beings in southeastern Massachusetts and Rhode Island. A considerable number of children and adults were affected.[1] In many cases the virus was identified as the eastern variety of equine encephalitis, although in some cases such an identification was not, or could not, be made. The present case falls in the latter group, since tests did not reveal a positive neutralization reaction. In a majority of the cases of the proved equine type, as well as in a number of the others, the patients did not survive, but in almost all, including the case reported here, the acute onset and initial symptoms were similar.

Of particular interest to us in connection with the present case has been the essentially parallel course of improvement in the clinical behavior, the electroencephalogram and the spinal fluid findings.

REPORT OF A CASE

History.—H. C., a Jewish boy aged 10, was well behaved and making excellent progress in school prior to the illness to be described. His intelligence quotient on a group test was 145. His health had always been good except for a mild attack of measles at 4 and again at 7 years of age, a mild attack of scarlet fever at 4 and chickenpox at 9. The family history was without significance.

On Sept. 10, 1938, he was admitted to the Beth Israel Hospital in Boston. Ten days before entry coryza had developed, with a temperature rising to 102 F. and persisting for two days. On the night of September 6 he was awakened with nausea and vomiting. There were profuse, watery diarrhea and a temperature of 102 F. The diarrhea and vomiting disappeared under treatment within twelve hours, but

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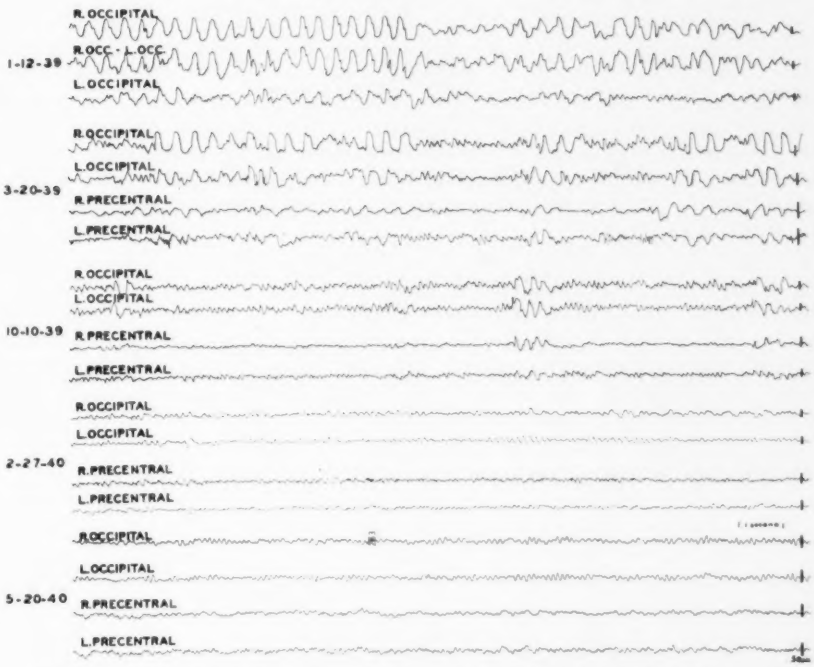
From the Emma Pendleton Bradley Home.

Research aided by a grant from the Rockefeller Foundation.

1. Fothergill, L. D.; Dingle, J. H.; Farber, S., and Connerly, M. L.: Human Encephalitis Caused by the Virus of the Eastern Variety of Equine Encephalomyelitis, New England J. Med. **219**:411 (Sept. 22) 1938. Wesselhoeft, C.; Smith, E. C., and Branch, C. F.: Human Encephalitis: Eight Fatal Cases with Four Due to the Virus of Equine Encephalomyelitis, J. A. M. A. **111**:1735 (Nov. 5) 1938. Farber, S.; Hill, A.; Connerly, M. L., and Dingle, J. H.: Encephalitis in Infants and Children, ibid. **114**:1725 (May 4) 1940.

a temperature ranging from 102 to 104.5 F. persisted. After two days in bed the temperature fell, and the patient seemed improved, but on the evening of September 8 his temperature again rose above 100 F. On the morning of September 9 the temperature reached 104 F., and a generalized clonic convulsion, lasting more than five minutes, occurred. That night he was irrational and had visual hallucinations. On the next morning he had another convulsion and was then sent to the Beth Israel Hospital, where he remained until discharged on Oct. 10, 1938.

Physical Examination.—On entrance to the hospital the child was toxic and irrational. The pupils and extraocular movements were normal. Ophthalmoscopic examination gave normal results. There was a mucoid discharge from the nose,



Typical samples from electroencephalograms at various intervals during recovery from encephalitis. The first record in the series, taken approximately four months after the onset of illness, shows marked abnormality. Subsequent records in the series show the transition from abnormal to practically normal activity, in the final record. This transition was associated with a reduction in the protein content of the spinal fluid and improvement in clinical behavior.

and the mucous membranes of the nose were injected. The lungs, heart and abdomen were normal. There was no retraction or stiffness of the neck. The Kernig sign was not elicited. The reflexes were equal and active throughout, except for a diminished left knee jerk. There were no other abnormal neurologic signs.

Laboratory Data.—Examination of the urine gave normal results. The blood count on admission showed 3,800,000 red cells, 68 per cent hemoglobin and 12,100 white cells, with 80 per cent polymorphonuclear leukocytes. The white cell count

rose to 18,000 on the fifteenth day in the hospital, coincident with low grade otitis media, but was normal on discharge. Blood cultures were sterile on two occasions. Examinations and cultures of the stool gave negative results. Agglutination tests for typhoid, paratyphoid and undulant fever were negative. Lumbar puncture on admission revealed normal dynamics, 7 lymphocytes per cubic millimeter, 45.3 mg. of total protein per hundred cubic centimeters, a slight trace of globulin and a sterile spinal fluid culture. The spinal fluid on September 15 showed 630 red blood cells and 8 lymphocytes per cubic millimeter, and on September 22, 1,100 red blood cells and 110 lymphocytes. Roentgenograms of the chest and long bones were normal.

Clinical Course.—On admission the temperature was 100.4 F., the pulse rate 125 and the respiratory rate 25. During the first two days in the hospital the temperature ranged from 103 to 105 F.; thereafter it fluctuated from 99.6 to 103.6 F. and returned to normal on September 29, except for slight elevations in the afternoon. On the fourth hospital day the patient had a clonic convulsion lasting ten minutes involving the left side, followed by complete left hemiplegia and partial left hemianesthesia. One hour later a clonic convulsion, lasting twenty minutes and involving the left side and right arm, occurred; it was interrupted by an intravenous injection of sodium amytal. After a third convulsion on September 23, the patient showed signs of slight left hemiparesis, with increased reflexes and a positive Babinski sign on the left.

From October 10 to 29 the patient remained in bed at home. During this time he ate and slept well and talked rationally, but continued to have slight fever in the afternoon. On October 29 there developed tremors of the left arm and leg, and he was unable to sleep. Sedatives had no effect, and he slept only for short intervals when exhausted. Gradually, after October 30, he became noisy, hyperactive and unable to concentrate. He also became destructive, impulsive and obscene. He cut holes in the wall with a knife, struck his mother and said unkind things to her, but on occasion became remorseful and apologetic for his acts. Because of his extreme hyperactivity and destructiveness at home he was sent to the pediatric ward of the Boston City Hospital, but his unmanageability there made it necessary to transfer him to the Boston Psychopathic Hospital, where he was admitted on November 7. Physical and neurologic examinations at this hospital gave normal results, except for a fine tremor of the extended hands, occasional coarse, irregular jerking movements of both legs and a questionable Babinski sign on the left. Several lumbar punctures during the next three months showed only slight elevation in pressure and normal dynamics. The spinal fluid findings were essentially normal, except for the total protein content, which ranged from 50 to 65 mg. per hundred cubic centimeters. A pneumoencephalogram on Jan. 27, 1939, showed no definite abnormality. In November 1938, an intelligence quotient of 118 was obtained with the Kent oral test, but its validity was questioned because of distractibility during the test.

Behavior during the four months' stay at the Boston Psychopathic Hospital was characterized by extreme hyperactivity, destructiveness, obscenity, assaultiveness, threatened suicide, temper tantrums, screaming and random expectoration and urination. At times he was quiet, cooperative and apologetic for misbehavior. During this period of four months there were at least eight severe convulsions, lasting from ten to twenty minutes. Between these episodes there were occasional twitchings of muscle groups and peculiar sensations in the extremities. Some reversal in the sleep cycle was noted, and there was a marked increase in appetite. During December 1938 he was given a short course of fever therapy with injections

of typhoid vaccine. These injections were discontinued, since they usually induced seizures. The patient was discharged on March 5, 1939, with slight improvement in behavior and fewer convulsive episodes.

On March 7, 1939, the patient was admitted to the Emma Pendleton Bradley Home presenting a severe postencephalitic behavior problem. Physical and neurologic examinations then and at intervals during the next year gave essentially normal results. Laboratory findings, including results of a dextrose tolerance test, were within normal limits, except that the total protein content of the spinal fluid on admission was 49.5 mg. per hundred cubic centimeters. During the next six months the total protein level gradually returned to normal (table).

Behavior in the hospital was characterized by variability. There were periods of irritability, noisiness, hyperactivity and impulsiveness. Benzedrine sulfate (20 mg. daily) made the child quieter and more cooperative. From May to September

Data on Patient Before, During and Following Encephalitis

Date	No. of Convulsions	Spinal Fluid Protein, Mg. per 100 Cc.	Per Cent of 2 to 4 per Second Abnormal Slow Waves						Intelligence Quotient	Behavior
			Occipital		Precentral		Frontal			
			Right	Left	Right	Left	Right	Left		
Prior to illness	0	....	..	..	..	..	..	..	145	Good
September 1938	5	45.3	..	..	..	..	..	..	...	Good
October 1938	?	55.0	..	..	..	..	..	..	...	Good
November 1938	2	65.0	..	..	..	..	..	..	118	Very poor
December 1938	3	....	..	..	..	..	..	..	...	Very poor
January 1939	1	52.0	81	52	69	42	51	35	...	Very poor
February 1939	2	....	79	..	61	..	50	..	...	Very poor
March 1939	0	49.5	50	35	24	21	10	12	134	Slight improvement
April 1939	1	59.5	..	..	..	..	..	..	...	Slight improvement
May 1939	0	....	..	..	..	..	..	..	...	Improved
June 1939	0	45.4	..	..	..	..	..	..	...	Improved
July 1939	0	37.7	..	..	..	..	..	..	...	Improved
August 1939	1	....	..	..	..	..	..	..	...	Improved
September 1939	0	26.7	..	..	..	..	..	..	148	Good
October 1939	0	....	10	6	0	7	0	0	...	Good
February 1940	0	....	10	0	0	0	0	0	145	Good
May 1940	0	39.2	5	0	0	0	0	0	...	Good

1939 there was definite improvement in behavior, with fewer periods of restlessness and irritability. The behavior from September 1939 until his discharge in June 1940 has been consistently good. Only two major convulsions occurred while he was at the Bradley Home: one on April 19, 1939, lasting fifty-seven minutes, and another on August 16, lasting twenty minutes. Both attacks involved chiefly the left side. Between these dates occasional minor episodes of twitching of extremities occurred, but there have been no attacks since August 1939.

Results of Psychometric Examinations and Progress in School.—School work has improved consistently since September 1939. The high quality of work and the general progress in school during the past nine months are comparable with those prior to the illness. Intelligence quotients have been computed for various tests administered before, during and in process of recovery from the illness. The results for verbal tests are included in the accompanying table. An intelligence quotient of 145 was reported on a group intelligence test (National) in 1938, before the onset of the illness. An intelligence quotient of 118 in the Kent oral emergency test was reported from the Boston Psychopathic Hospital in November 1938. On admission to the Emma Pendleton Bradley Home, in March 1939, the following

intelligence quotients were obtained: form L, Stanford-Binet, 134; Kuhlmann-Anderson (nonverbal), 114; Arthur performance test I, 108. Subsequent testing in September 1939 revealed an intelligence quotient of 148 on form M, Stanford-Binet, and a rating of 122 on the Arthur performance test II. In March 1940 an intelligence quotient of 145 was obtained on form L, Stanford-Binet, and one of 150 on the Kuhlmann-Anderson test. These results show a general decrement in intelligence quotients on verbal, nonverbal and performance tests during the illness and an increase in scores on all tests during recovery.

Electroencephalographic Data.—The striking changes in the electroencephalogram over a period during the recovery are shown in the accompanying figure. The first record in this series was obtained by Dr. Knox Finley, of the Boston Psychopathic Hospital, in January 1939, four months after the onset of the illness. The records at this time showed gross abnormality in the form of large, 2 to 3 per second, slow waves in all regions of the head, with the most severe disturbance in the right occipital area. Normal alpha waves were almost completely absent. The abnormal slow waves appeared in short bursts and persistent sequences.

Electroencephalograms obtained at the Bradley Home in March 1939 showed patterns of slow waves, 2 to 4 per second, similar to those found in the preceding records, but the bursts and sequences were less persistent. The records obtained in September 1939 still showed short bursts of slow waves, but they were markedly diminished in amplitude and amount, and there was a considerable return of the normal alpha rhythm. In February and May 1940 the patterns of activity were practically normal in all regions of the head except the right occipital area, where there were still rare, but brief, bursts of slow waves of low amplitude.[2]

The table shows the percentage of abnormal slow waves in the various regions of the head for the entire series of records. It will be noted that between March 1939 and October 1939 there was a great reduction in the percentage of abnormal slow waves. This interval, during which the most marked change in the electroencephalogram toward normality occurred, coincides with the period during which the total protein in the spinal fluid decreased and a striking improvement in behavior became apparent.

COMMENT

Two relationships involving the electroencephalogram are suggested by the results reported here. One is concerned with the apparent association of the abnormal slow waves of the electroencephalogram in this case with active processes of destruction of nerve tissue, and disappearance of the slow waves and return of normal patterns of activity with diminution in these processes, as evidenced by a reduction in the total protein content of the spinal fluid. Just how extensive these processes of destruction were cannot be said, although it appears from the amount of abnormal slow waves in all regions of the head in the early records that the disturbances were rather widespread. The disturbances were apparently less severe in the anterior regions of the head and first disappeared completely there. Whatever the nature of the destructive

2. The patient was seen again on Sept. 16, 1940. His health and behavior during the preceding three months had been good, and he was attending public school. Electroencephalograms at this time were normal except for rare, usually single, slow waves (less than 2 per cent) of low amplitude in the right occipital region. Results of examination of the spinal fluid were within normal limits; the total protein content was 38.8 mg. per hundred cubic centimeters.

processes may have been, they seem to have left no residual defects that can be observed in behavior or performance on mental tests at present. The fact that areas of destruction in the cortex, in this case presumably small and scattered, may remain, although the electroencephalogram has returned essentially to normal is not inconsistent with other findings, for it has been shown by Walter [2a] and by Schwartz and Kerr [3] that cortical areas invaded by tumor and scar tissue are electrically inactive and that the slow waves presumably arise from the bordering regions in process of deterioration or secondarily affected.

The other relationship has to do with the association of abnormal activity in the electroencephalogram and the behavior symptoms. With the disappearance of the abnormal slow waves the behavior steadily improved. Elsewhere,[4] in other types of cases in which there was freedom from physical and neurologic signs we have called attention to the association of abnormal slow waves in the electroencephalogram with behavior disorders.

SUMMARY

A case has been described in which disturbances in behavior subsequent to an attack of encephalitis in a child aged 10 disappeared along a course more or less parallel with the reduction of protein in the spinal fluid to a normal level and the return of the electroencephalogram to an essentially normal state.

The Beth Israel Hospital of Boston and the Boston Psychopathic Hospital furnished many of the clinical data included in this report. Dr. Knox Finley, of the Boston Psychopathic Hospital, permitted the use of his electroencephalographic data.

2a. Walter, W. G.: The Electro-Encephalogram in Cases of Cerebral Tumor, Proc. Roy. Soc. Med. **30**:579 (March) 1937.

3. Schwartz, H. G., and Kerr, A. S.: Electrical Activity of the Exposed Human Brain, Arch. Neurol. & Psychiat. **43**:547 (March) 1940.

4. Lindsley, D. B., and Cutts, K. K.: Electroencephalograms of "Constitutionally Inferior" and Behavior Problem Children: Comparison with Those of Normal Children and Adults, Arch. Neurol. & Psychiat. **44**:1199 (Dec.) 1940.

Obituaries

H. DOUGLAS SINGER, M.D.
1875-1940

On the way to his ranch and vacation, Dr. H. Douglas Singer met with an automobile accident on Aug. 9, 1940, and appears to have had some internal injury leading to pulmonary embolism, which recurred and carried him off in the midst of apparently safe convalescence, on Aug. 28, 1940.

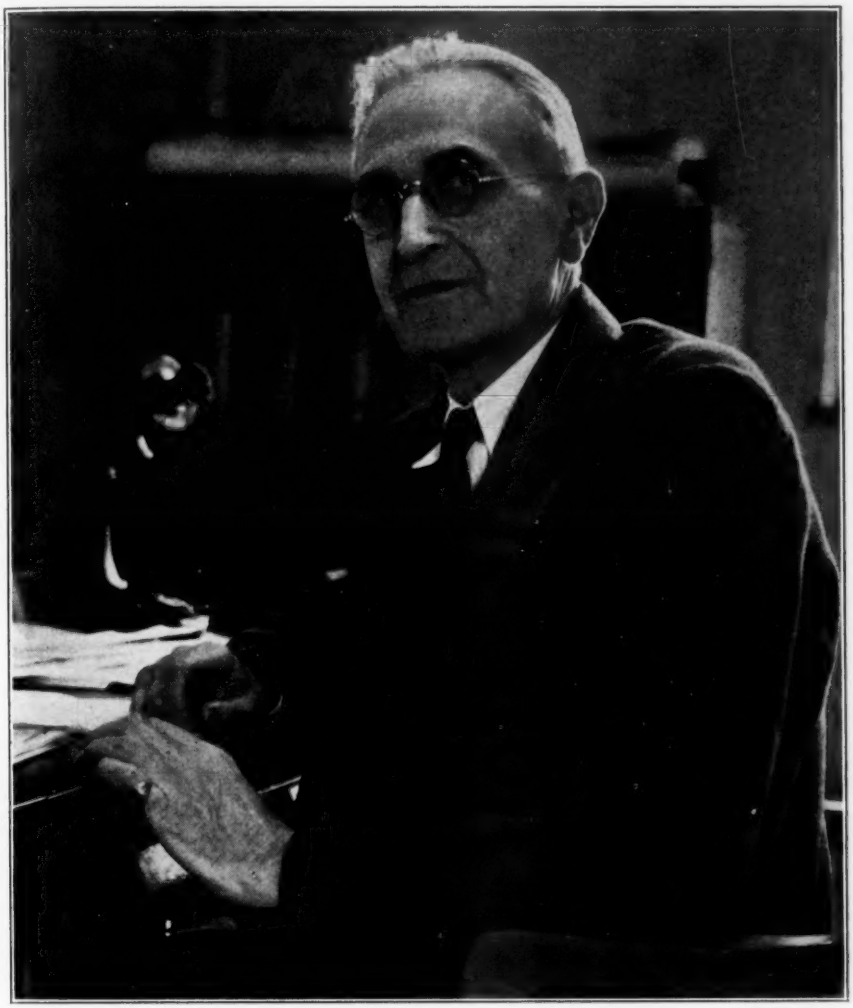
The two leading national societies of neurology and of psychiatry had elected Dr. Harold Douglas Singer to preside over this year's meetings. He was the president of the American Board of Psychiatry and Neurology and Chief Editor of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. These and the department of psychiatry of the University of Illinois will miss him sorely.

A tall, well built man of quiet manner and measured judgment, capable of a large amount of administrative work, Dr. Singer was a strong factor in the organizations to which he belonged. He had the full confidence of the officials of the American Medical Association and of the state authorities, as well as of neurologists and psychiatrists throughout the world.

His personality and his whole makeup presented that same mellow and quiet determination which accounts for the even course of his career—unostentatious but firm and dependable, with clear and discriminating decision and policy, in manner and performance. The harmony between his inner life and his professional career was obvious from his bearing. He displayed relatively little urge toward public expression or writing, but his few publications show the excellent basic character of his English medical training.

Born in London in 1875, he laid his general medical and neurologic foundations in St. Thomas's Hospital, to which he returned after a residency in the National Hospital of London. On his arrival in the United States of America in 1904 he became associate professor of neurology in Creighton University School of Medicine, Omaha, and served in the Norfolk (Neb.) State Hospital. Later, he became associate professor in the University of Nebraska College of Medicine. With this experience he entered the state service of Illinois as head of the Psychopathic Institute of Kankakee, Ill., in 1907, then assumed leadership of the state service as state alienist and from 1919 served as pro-

fessor of psychiatry of the University of Illinois. In this position he was just about to reap the fruit of his endeavors in opening one of the best organized teaching and research hospitals available in this country, largely the result of his own planning and influence.



H. DOUGLAS SINGER, M.D.
1875-1940

His early writings were strictly neurologic, including also histologic work on myelitis (1902) and pellagra (1913). But that with his expansion into psychiatry he developed a clear appreciation of the dynamic factors in the psychoneuroses and psychoses, with a sound

critical reserve, is shown, for example, in his paper "Is Dementia Praecox Properly Described as an Infantile Mode of Reaction?" (1916). Nevertheless, in discussions of the teaching of psychiatry he was reluctant to give any quarter to the psychopathology and therapy of actual psychoses, allocating treatment to the sphere of the internist. His basic English training in regard to mental disease remained fundamental to his point of view. He stood valiantly for the dynamic character of psychology without, however, taking a definite stand on specific definitions of basic concepts. This was his method of keeping a sympathetically open mind toward various factions among neuropsychiatrists and a certain aloofness toward those who took too specific an attitude.

Dr. Singer served as chairman of the Committee on Mental Health and as chairman of the Section on Nervous and Mental Disease of the American Medical Association; in this capacity and in the editorial work of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY, as its second editor, he made himself invaluable by his fair judgment and administrative ability.

An able leader, widely respected and warmly admired, has been torn from the profession. It will be impossible to replace him, and he will be greatly missed.

ADOLF MEYER, M.D.

Abstracts from Current Literature

Psychiatry and Psychopathology

PHANTOM FORMATION IN A CASE OF EPILEPSY. FRITZ WITTELS, Psychoanalyt. Quart. **9**:98, 1940.

Wittels discusses the intrapsychic problems in a case of epilepsy. The patient had a number of conflicting unconscious wishes, which Wittels designates as fantoms. These were: (1) a desire to be on intimate terms with, i. e., a feminine pal of, two former friends of his; (2) a wish to be a superior person to these friends; (3) a wish to be a woman—he felt he had been made a woman when seduced by one of these two friends; (4) a wish to reject his brother, as the latter had rejected him by not speaking to him for a year after a quarrel provoked by the brother; (5) a wish to have a feminine relationship with his father; (6) a hatred of his father, and (7) a wish to have an intimate relationship with his sister.

Whenever any of these conflicting wishes were exposed, the number of epileptic attacks increased. When the conflicts were made conscious or when circumstances ameliorated them, the attacks became less.

Wittels points out that although psychotherapy cannot cure epilepsy, it may reduce the number of seizures by removing the psychoneurotic superstructure.

PEARSON, Philadelphia.

CRIMINOLOGY AND PSYCHOANALYSIS. ATWELL WESTWICK, Psychoanalyt. Quart. **9**:269, 1940.

Westwick pays tribute to Freud's contribution to the understanding of crime and delinquency. Freud demonstrated that crime and delinquency are only symptoms of personal and social maladjustment, that their causes can be discovered and remedied and that all offenders, regardless of the particular offense committed, if they must be confined at all, should be confined indefinitely until it is safe to release them, just as one confines the dangerously insane, the feebleminded or those who suffer from contagious disease. While parole, probation and the juvenile court are really promising innovations in the field of criminology, their effectiveness in dealing with criminal and delinquent activity is seriously curtailed and hampered by the failure of those who administer them to grasp the true significance of what underlies and motivates human behavior and the utter necessity of a comprehensive program of preventive therapy. Traditional administration of criminal justice, unfortunately, is still dominated by the idea that the law is an inflexible body of rules which, by punishing offenses, places a highly desirable and necessary emphasis on principles of retaliation, retribution, atonement, expiation and determent. But however ingenious and inhuman the penalties, the number of offenders seems never to have decreased, and centuries of punishment, except for the savage satisfaction of vindictiveness, have accomplished nothing for the human race. Retribution, retaliation and expiation were historically the first principles on which society proceeded against offenders. The next development, after many centuries in which the primary effort was deterrence, was a period of repression of crime by intimidation and torture. The law fixed minimum penalties only and left it to individual judges to add such additional punishment as they pleased. The exercise of this tyrannical power by judges over the course of the years led to such horrible abuses that the classic school of criminology arose as a protest. Thought then turned somewhat to the idea of reformation. The classicists, saturated with the political philosophy of the eighteenth century, insisted that legislators, not judges, should define the crimes and fix the punish-

ment. They did not attack the medieval idea that man is a "free moral agent" and therefore entirely responsible for his acts. They insisted that the same punishment should be visited indiscriminately on every person who committed the same act, regardless of circumstance, age, mental or emotional condition. In time, naturally, society saw that it must exclude from this system of fixed punishment those persons who by reason of youth, insanity, idiocy, and the like, were patently incapable of exercising "free will." At last there began to develop recognition of extenuating circumstances in the offender himself. Next developed the "positive school of criminology," led by Caesar Lombroso, who advanced anthropologic and psychiatric explanations for criminality and substituted science for philosophy and theology in the field of criminology. It remained for Freud to provide an approach which not only combined with discrimination what was valid in these interpretations, but evolved also a scientific discipline dealing with the psychologic, dynamic forces within the human being, whether the manifestation of these forces was socially acceptable, such as literary and artistic expression, or whether it was mental disease or criminal behavior. Much criminal behavior is utterly irrational and so deeply rooted in the unconscious that without psychoanalysis its meaning and causes and the corrective possibilities involved are entirely beyond the ken and reach of judges, probation officers, social workers, teachers, wardens, prison directors, psychologists, "mental testers" and large numbers of clinical psychiatrists. Society continues, however, to punish most of its offenders. In the United States, about 1790, there was substituted for corporal punishment the Pennsylvania, or separate, system of imprisonment. Here the chief aim of incarceration was penitence. Later, in the first quarter of the nineteenth century the Auburn, or silent, system urged the value of work in silent association by day and solitary confinement by night. Around 1850 developed the Elmira system, based on the idea of classifying offenders according to behavior, with efforts at improvement during confinement. The aim appeared of treating the prisoner rather than the crime, of protecting society by reforming the offender. The gradual diffusion of this principle brought into existence, around the beginning of the twentieth century, parole, the indeterminate sentence, probation and the juvenile court. But there is nowhere any really wise application of the resources of psychoanalysis to the problem of reformation and rehabilitation.

Freud's contribution was to point out the existence of fundamental urges in the person, and to show that interferences with these fundamental wishes are felt "as thwartings and deprivations causing keen dissatisfaction," which are met or balanced by substitutive satisfactions. Often these substitutes take the form of crime or delinquency when the person has been unable, by reason of faulty habit formation or training, to find socially acceptable substitutive satisfactions. The whole purpose of modern criminology, including prisons and other institutions, being the protection of society, the best way to accomplish this objective is to reform the criminal or, if he cannot be reformed, to keep him confined. The way to reform is to educate, and the way to educate is to psychoanalyze. For those already delinquent, society, when it becomes better informed, will insist on psychoanalytic clinics and hospitals, with prison farms, colonies and the like, built, equipped and conducted in the modern spirit. That great numbers of persons will have to be confined for the duration of their lives in one type of institution or another goes without saying. But it is just as certain that a significantly high percentage of offenders definitely can be healed and saved if society will go to the expense and take the time and trouble to do it. That the carrying out of this suggestion would involve expensive and comprehensive education in psychoanalytic concepts and technics for parents, teachers, social workers, judges, probation officers and all others who presume to deal with the problems of misbehavior is a no more valid objection than might be raised against education in any other important field or phase of human endeavor.

PEARSON, Philadelphia.

PREEDIPAL PHASE OF LIBIDO DEVELOPMENT. R. M. BRUNSWICK, Psychoanalyt. Quart. **9**:293, 1940.

Brunswick states that although Freud formerly believed that the Oedipus problem was the nuclear complex of the neuroses, he latterly inclined to the view that the preoedipal period was as important as the Oedipus complex. Brunswick, as a result of studies of her own and her consultations with Freud, puts forward the following views: In the preoedipal period there is an exclusive libidinal attachment between the child of either sex and the mother. In boys this preoedipal period is shorter than in girls. In the latter the preoedipal attachment to the mother develops into an active oedipal attachment, with the wish to give the mother sexual pleasure and a child and a rivalry with the father. This active oedipal phase is destroyed by the discovery of castration, which means that the girl cannot give her mother sexual pleasure or a baby, and out of this destruction the little girl develops a passive Oedipus attachment to the father, with the wish that he give her sexual pleasure and a baby, and a rivalry with the mother. While the Oedipus complex is destroyed in the boy, the little girl tends to remain in an Oedipus situation. The girl has to adjust to two love objects—the mother and the father—and to two sex organs—the clitoris and the vagina—the boy has only to change his passive attitude to his mother into an active one.

There are three great pairs of antitheses in development: In infancy there is the antithesis of active and passive attitudes, in childhood that of phallic and castrated ideas and in adolescence that of masculine and feminine. In the stage of the first pair each bit of activity is brought out through an identification with the mother, who at this stage is active to the passive child. This ability to replace passivity with activity is more vigorous in boys than in girls. The earliest abnormality is an inability to substitute activity for passivity. The inability may be partly constitutional, but also is due to the fact that the mother's activity tends to restrict that of the child. The latter reacts to this by defensive aggression. This aggression is a by-product of activity and of a defense against the barely overcome passivity and is increased by the early narcissistic injuries—weaning, birth of a new sibling, relation between mother and father, sexual rejection by the mother and her threats of castration. The conflict between the wish to be passive to the mother and the wish to be active and aggressive must be solved by the repression of the aggression, but often the activity is also repressed simultaneously.

The interest in the genitals and the discovery of sexual differences coincide with a biologic push toward the phallic period about the end of the third year. This period is characterized by predominantly active and some passive desires to the mother and by phallic masturbation (masturbation of the clitoris in the girl). The boy passes easily into the active Oedipus situation, but the girl's activity is still preoedipal. When the genital libido is at its height, the mother's castration is perceived and acknowledged, and because her castration is a threat to him, the boy abandons his desire for his mother and his rivalry for his father and turns his activity into the formation of his superego and his sublimations. The sight of the mother's castration causes an implied threat to his own penis and the destruction of the male Oedipus complex.

To the little girl the sight of the mother's castration causes the child to depreciate her as a love object and to fear her own castration and denies to her the hope of ever having a penis. These operate to compel her to abandon her activity toward her mother with bitterness, more intense than that which the boy feels. She seeks to transfer her libido to the father, but this is difficult because of her tenacious active and passive attachment to her mother. The passive strivings as an identification with the castrated mother are transferred to the father, and the active strivings are sublimated and only again find real expression in relation to her own child. In the regression which accompanies the acceptance of castration it is possible to observe clearly strivings from the oral and anal stages.

Between the stage of the girl's attachment to her mother and that to her father there is a brief preoedipal period of latency. At adolescence the attachment to the father is reenforced by the wave of passive libido called forth by the menses and the awakening of vaginal sensation.

The relation of the child to the mother is the fundamental of psychic life. The first attachment to her is passive and draws strength from the physical care she gives the child. In order to be active the child does as the mother does. The primal scene fantasy which occurs at the Oedipus period is understood in the light of the child's earlier experiences at the hands of the mother. The child believes that in sexual relations the mother does to the father what she did to him as a baby; i. e., the active mother may suckle the passive father or the active father may suckle the passive mother.

Children often show rage when there is any stimulation of the anal zone. This is because the awakening of the anal zone corresponds in point of time with the production of intense aggressive impulses. It would appear that rage is the true motor expression of anal eroticism, as an orgasm is of genital eroticism.

The desire for a baby starts originally as a desire to be like the mother and to possess everything possessed by her. In the anal phase the desire is to receive a baby from the mother or to give her a baby. In the phallic phase the boy gives up the passive wish to be given a baby by the mother, identifies with the father and desires to give the mother a baby. The girl gives up her active wish for a baby when she accepts castration and her inability to impregnate the mother.

There are three types of infantile activity: (1) identification with the all-powerful mother; (2) identification with the oedipal father (the girl is incapable of making this identification successfully), and (3) the idea of being a sexually undifferentiated person, like a page girl in an opera. The little girl's wish to have a penis has an object root when she realizes she cannot win her mother without a penis. Usually the relinquishment of the active wish to have a penis and the attachment to the mother coincide. The wish to have a penis is not exchanged for the wish to have a baby because they coexist at the same time.

The little girl represses her infantile sexuality enormously—to a much greater degree than does the boy. The female distaste for masturbation arises from the fact that touching the genitals reminds her of her castrated state. This also is the reason why girls give up manual masturbation earlier and more completely than boys. The little girl does not have as much contempt for the castrated mother as the boy does because she and the mother are alike, but she has great bitterness toward her mother. The original clitoral masturbation has active fantasies which are directed to the mother. The original role may be repressed and clitoral masturbation continued with passive fantasies, or both the active fantasies and the clitoral masturbation may be repressed; a great attachment to the father ensues because the repression acted on both the original masturbation and its direction to the mother.

In both sexes a great difficulty in development is the early presence of too great passivity, which is unresolved and unassimilated. In the boy the obstacles to active oedipal identification with the father are: (1) a nuclear passivity; (2) an undue amount of aggression to the mother, and (3) inability to accept the mother's castration.

PEARSON, Philadelphia.

NEUROSES AMONG COMBATANT TROOPS IN THE GREAT WAR. F. DILLON, Brit. M. J. **2**:63 (July 8) 1939.

Statistics from the last war showed that one third of the unwounded in the British army and one seventh of those discharged were permanently unfit because of functional neuroses and mental disorders. During the twenty-two month period preceding October 1918, 4,235 patients whose adaptation to active war conditions had broken down were treated by the author. Seventy per cent of these patients fell into the group who exhibited fear or anxiety symptoms, 20 per cent manifested conversion symptoms and the remaining 10 per cent displayed mental confusion, amnesia or war neurosis combined with an organic disorder. In the largest group no special form of treatment was employed, and all of the men were able to return to duty after about forty-eight hours' rest. The fear and anxiety were the commonest form of shell shock and comprised the usual residual state after other forms

of neuroses had cleared up. It was observed that in the cases of amnesia memory returned spontaneously after four or five weeks. Of the total series, 63.5 per cent were able to return to duty after treatment, which consisted primarily of rest and sleep. Relapses occurred in 5 per cent of the cases. The author was unable to estimate the part predisposition played as an aid in prognosis.

ECHOLS, New Orleans.

NERVOUS DISORDER AFTER INJURY: A REVIEW OF FOUR HUNDRED CASES. J. RAMSAY, Brit. M. J. **2**:385 (Aug. 19) 1939.

In Ramsay's series of 400 cases of injury, the age, sex and severity of the injury were not germane to the subsequent development of functional nervous disorders in 41 per cent of cases. The author believes that in these instances some maladjustment was already present and that the injury was merely an exciting cause of the subsequent psychoneurotic symptoms.

Cases of neuroses following injury in this series are classified as those of hysteria (62 per cent), postconcussion syndrome (23 per cent), neurasthenia (10 per cent) and anxiety state (5 per cent). The prognosis of the postconcussion syndrome is more favorable than that of any of the other three types.

The author believes that subsequent neuroses can be prevented largely by the adoption of an optimistic and sympathetic attitude by the physician in charge. Mental exploration and rest in bed are advocated in treatment. The financial settlement of a claim may be made a useful adjunct to other therapy. In a discussion of the legal aspect of the subject, the author emphasizes the importance of impartiality on the part of the physician.

ECHOLS, New Orleans.

Diseases of the Brain

TOXOPLASMIC ENCEPHALOMYELITIS. A. WOLF, D. COWAN and B. H. PAIGE, Am. J. Path. **15**:657, 1939.

A fifth case of a new disease, granulomatous encephalomyelitis due to a protozoon, occurring in an infant is described. The clinical and pathologic observations in this case are shown to be similar to those in the first 4 cases. This group represents a distinct disease entity. The disease affects young infants, produces manifestations of general involvement of the nervous system, may give rise to ophthalmoscopically identifiable focal lesions in the eyegrounds and terminates fatally after an acute or subacute course. The spinal fluid shows xanthochromia, a high protein content and pleocytosis. The central nervous system is the site of focal inflammatory and degenerative lesions, which are widely disseminated. Similar changes are found in the retina and choroid. Miliary granulomas are a characteristic feature of the process in the nervous system. Focal inflammatory lesions were present in the heart and striated muscle in 1 case. A protozoan parasite is present in all the lesions. The results of transmission of the infection to animals in the case reported here indicate that the causative protozoon is a species of Toxoplasma. The designation Toxoplasma hominis is suggested for the micro-organism and the term "toxoplasmic encephalomyelitis" for the disease.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

SIGNIFICANCE OF APHASIA AS A SYMPTOM OF OTOGENIC EXTRADURAL ABSCESS. FRANZ ALTMANN, Arch. Otolaryng. **31**:819 (May) 1940.

Aphasia is said to be the most frequent symptom of abscess of the left temporal lobe. Aphasia disappearing after evacuation of an extradural abscess has been reported a number of times. In 1 instance a remaining temporal abscess caused death a year later. Pressure does not always explain the aphasia. Altmann reports 2 cases in which aphasia was present with an extradural abscess, the

result of chronic purulent otitis media. In cases in which the external pressure prevails or in which inflammatory changes are slight or absent the diagnosis of extradural abscess can be established with a certain degree of assurance. In cases in which the inflammatory factor predominates the differentiation from abscess of the brain becomes practically impossible. Aphasia without increased intracranial pressure makes the diagnosis of abscess questionable and favors the diagnosis of extradural abscess.

HUNTER, Philadelphia.

EXPERIMENTAL TRANSMISSION OF TOXOPLASMIC ENCEPHALOMYELITIS. A. WOLF, D. COWAN and B. H. PAIGE, J. Exper. Med. **71**:187 (Feb.) 1940.

Wolf and his co-workers encountered a case of granulomatous encephalomyelitis due to a protozoon. They transmitted the infection to 3 rabbits and 6 infant mice and identified the causative micro-organism as a species of Toxoplasma. The authors state that a parasite identical with that in the lesions in the patient was found in the lesions of the experimental animals. The morphologic character of this micro-organism, the course of the disease and the lesions produced in the animals inoculated with it, the wide host range of this parasite and the results of cross immunity experiments, establish its identity as a species of Toxoplasma. It is suggested that the micro-organism be designated as Toxoplasma hominis. The infection in the infant is the first proved instance of human toxoplasmosis. Since the lesions were confined to the central nervous system, the disease is termed toxoplasmic encephalomyelitis. This paper records the first experimental transmission of human toxoplasmosis to animals.

J. A. M. A.

DELAYED TRAUMATIC INTRACEREBRAL HAEMORRHAGE. C. P. SYMONDS, Brit. M. J. **1**:1048 (June 29) 1940.

There are two varieties of delayed traumatic apoplexy: early and late. Both are extremely rare. In the early variety the hemorrhage occurs within a few weeks of the injury, probably as the result of traumatic weakening of an arterial wall. Blood is often found in the ventricles and cerebrospinal fluid. The clinical picture may resemble closely that of a ruptured congenital aneurysm. In the late variety the interval between injury and apoplexy may be several months or years. The mechanism is hemorrhage into a cyst resulting from intracerebral hemorrhage at the time of the injury. The clinical symptoms are usually those of cerebral hemorrhage.

Delayed symptoms may be due to an intracerebral hemorrhage, dating from the time of the injury, as the result of cyst formation with progressive increase in volume—chronic intracerebral hematoma. The symptoms then resemble those of a cerebral tumor.

ALPERS, Philadelphia.

RELATION OF THE SCHÜLLER-CHRISTIAN SYNDROME AND EPILEPSY. T. FRACASSI, Rev. argent. de neurol. y psiquiat. **4**:135, 1939.

Fracassi reports the case of a boy aged 14 years, who was born at term. There was 1 brother, 4 years older, who was well. The mother had had three spontaneous abortions. At the age of 5 the patient had measles, after which he displayed abnormal thirst; he sometimes drank as much as 20 liters of fluid a day. At this time two tumors appeared on his head, one in the frontal and the other in the occipital region. A little later there developed stomatitis and gingivitis, with formation of pus and rupture through the face, leaving a draining sinus that was still present at the time of the report. There slowly developed left exophthalmos and some character changes; he became irritable and unruly. He was unable to progress beyond the first grade in school. It was noticed that body development was retarded. He was treated with five hundred injections of insulin during this time, with some generalized improvement, the polydipsia decreasing to 4 or 5 liters a day. Two years before examination he began to have epileptic attacks.

Examination revealed that he was short and slight for his age (1.35 meters in height and 36.5 Kg. in weight). There was lack of normal development of the genitalia (infantilism). The face was asymmetric, being more developed on the left, with exophthalmos in the left eye (right eye 14 mm.; left eye 17 mm.), and the left palpebral fissure was wider than the right. No further abnormality was found in the cranial nerves. Examination of the scalp and skull gave normal results, with no evidence of the tumors described several years before. Mentally, the patient was irritable and irascible; the Binet-Simon test gave a mental age of 6 years. Examination of the mouth showed slight suppurative stomatitis. The neck and chest were normal, as was the abdomen. Neurologic examination otherwise gave normal results. Examination of the urine showed no cholesterol. The blood cholesterol was 1.20 and 1.40 Gm. per hundred cubic centimeters, respectively, on two occasions. The total lipid content of the blood was 6 Gm. per hundred cubic centimeters. On one occasion leukocytosis, with a count of 26,000, was noted; later the white count was normal.

Roentgenograms taken two years previously showed several defects in the skull, which were almost healed at the time of the report.

There can be little doubt that this is a case of the Schüller-Christian syndrome, as shown by diabetes insipidus, gingivitis, exophthalmos and defects in the skull. The epileptic attacks, since they persisted after disappearance of the tumors of the skull, are probably of the hypophysial type and are not due to xanthomas of the cortex. Direct involvement of the infundibulohypophysial area by accumulations of swollen cells would produce the diabetes insipidus and infantilism.

NORCROSS, San Francisco.

ENCEPHALITIS IN THE COURSE OF WHOOPING COUGH. F. BAZÁN and R. MAGGI, Rev. Asoc. méd. argent. **53**:1171 (Dec. 30) 1939.

Bazán and Maggi report their observations made from 1936 to 1939 in the department of infectious diseases of a pediatrics hospital in Buenos Aires, Argentina. Of 600 children with whooping cough, 15 (11 infants and 4 children ranging in age from 3 to 6 years) had acute encephalitis, as a rule in the third week of the illness. The authors found that the course of encephalitis complicating whooping cough varies with the age of the patient, the clinical form and type of encephalitis and the presence or absence of bronchopneumonic complications or otitis. The younger the patient the graver the nervous complications. These may be acute, subacute or chronic, with predominance of convulsions, somnolence, paralysis, polyneuritis, ataxia, choreoathetosis, poliomyelitis and sensory and psychic disturbances. Convulsive forms are the most frequent. The cerebrospinal fluid either is normal or shows a moderate lymphocytic reaction. The prognosis is grave (a mortality rate of 80 per cent in severe forms of encephalitis and the development of psychic, motor or associated psychomotor sequels in 50 per cent of cases of the subacute form). The condition is due to a toxic infection, the nature and mechanism of which are not clear. The treatment consists of administration of drugs to control convulsions, the general toxic infection and associated infections, baths, antispasmodic drugs, anesthetic, lumbar puncture for the convulsion, methenamine or a combination of cinchophen and methenamine, intravenous administration of hypertonic solution of dextrose, colloidal metals, protein therapy, abscess fixation and sulfanilamide. Associated infections are treated and vaccines against whooping cough are administered according to indications. It is advisable to watch and stimulate the functions of the cardiovascular system and to improve the organic resistance of the patient. If sequels remain, massage, electrotherapy, gymnastics and psychic reeducation are indicated. In the group of cases reported by the authors 12 patients died (all but 1 of whom were infants). Necropsies performed in 9 cases demonstrated that the pathologic lesions are not typical for whooping cough. They consist of degeneration, inflammation and hemorrhages. J. A. M. A.

FAMILIAL INFANTILE FORM OF DIFFUSE CEREBRAL SCLEROSIS (KRABBE). C. DE LANGE, Ann. pædiat. **154**:140 (Dec.-Jan.) 1939-1940.

Scarcity of reports of cases of the familial infantile form of diffuse cerebral sclerosis, first described by Krabbe, suggests that such cases are rare. Lange believes that a better knowledge of the symptomatology, with its many characteristic aspects, might lead to the recognition of a greater number of cases of this disorder. She reports the histories of 4 children in one family who successively manifested the same cerebral syndrome of general rigidity, opisthotonos and deterioration of intelligence. The first child, a girl, died at the age of 8 months; then there were twins (girls), 1 of whom died at 13½ months of age. The author was able to examine the brain of this child. The brain presented some congenital abnormalities. Moreover, there was diffuse demyelination of the entire cerebrum and of the parts of the spinal cord available for examination. There also existed extensive proliferation of normal and of pathologic neuroglia. The degree of fibrosis differed in various parts of the nervous system. The nerve cells were more or less intact. Some aspects pointed to a primary disease of the neuroglia. The author reviews cases from the literature and compares them with the familial juvenile form (Scholz) and with other leukodystrophies. More cases will probably be discovered if the following characteristic symptoms are kept in mind: familial occurrence, onset of illness usually a few months after birth, increasing general stiffness, often crossing of the legs (scissor position), opisthotonos, manifestations simulating spasmophilia and deterioration of the intelligence. The intracranial pressure is not increased.

J. A. M. A.

TRAUMA TO THE BRAIN STEM AND THE PROBLEM OF CEREBRAL CONCUSSION. E. BAY, Deutsche Ztschr. f. Nervenh. **149**:274, 1939.

Bay reports the case of a boy who was injured while fencing; the foil entered the medial angle of the right orbit, without producing demonstrable fracture of the orbit, injured the third, fourth and fifth nerves temporarily and produced symptoms of severe concussion, i. e., euphoria, amnesia and disturbance of sleep regulation, without unconsciousness, and severe transient paresis of the contralateral side of the body, including the lower part of the face. Bay believes that the nerves to the muscles of the eye were injured peripherally, perhaps at the cavernous sinus. The injury to the pyramidal tract occurred in the superficial area, at the junction of the pes pedunculi and the pons.

Bay points out that the diagnosis of localized traumatic lesions of the brain stem can be made and that the symptoms of concussion, when they follow such an injury, come at a longer interval after the injury than do symptoms following cortical trauma.

LOWIS, New York.

Peripheral and Cranial Nerves

SCALENUS ANTICUS SYNDROME WITH AND WITHOUT CERVICAL RIB. J. H. DONALD and B. F. MORTON, Ann. Surg. **111**:709 (May) 1940.

Donald and Morton studied 21 patients with the cervical rib and scalenus anticus syndrome. Of the 16 patients that have already received operative treatment, 13 were without cervical ribs, 2 showed supernumerary ribs and 1 presented an abnormal first rib. This indicates that the scalenus anticus syndrome occurs much more frequently than do cervical ribs. Two of the remaining 5 patients, on whom operation has been temporarily postponed, showed roentgen evidence of a cervical rib. The ages of the 21 patients ranged from 15 to 54 years, with an average of 37 years. The majority were in the fourth (9) and fifth (5) decades of life. Direct trauma preceding the onset of symptoms could be demonstrated in only 1 of the 21 cases. In 2 others the trauma was attributed to faulty position while the patient was under anesthesia, followed immediately by the development of symptoms typical of the syndrome. Excessive occupational strain was a significant

factor in 8 cases. The preponderance of cases in the fourth and fifth decades may possibly be attributed to regressive muscular changes that occur at this time and result in drooping of the shoulders. The characteristic increase of pain at night may be accounted for by pressure from behind as the shoulders are brought forward against the scalenus anticus muscle while in the prone position. The symptoms of the cervical rib and scalenus anticus syndrome are similar; in view of the fact that the scalenus anticus muscle is the primary factor in the production of neurocirculatory compression, whether a cervical or an abnormal first rib is present, it seems appropriate to group the two conditions under the term "scalenus anticus syndrome," designating whether a cervical rib or an abnormal first rib is present. The surgical indications (scalenotomy) are the same, and results are usually excellent. Fourteen patients have had complete relief from symptoms. Scalenotomy is not indicated in all cases, as in many the disturbance is mild and will respond to conservative therapy. The symptoms in cases of the milder form are not progressive, but are subject to remissions and exacerbations. Because of the frequent gradual onset and bizarre picture a positive diagnosis is often difficult. A neurologic examination is indicated in all cases. Conditions causing difficulty in the differential diagnosis are infectious neuritis, arthritis of the shoulder joint, cervical arthritis, subacromial bursitis and neurosis. J. A. M. A.

CERVICOBRACHIAL SYNDROME. K. H. AYNESWORTH, Ann. Surg. **111**:724 (May) 1940.

Aynesworth believes that the Naffziger limitation of the scalenus syndrome to neuritis of the brachial trunks is too narrow and that the symptoms of involvement of the vessels and nerve trunks should be expressed by a more inclusive term. The term "cervicobrachial syndrome" does not define the disease, but it does give a comprehensive and an anatomic concept which is accurate and inclusive. The author has observed 20 cases in which the diagnosis was confirmed by operation or subsequent history. Sixteen of these patients have come under observation since the role of the scalenus anterior muscle has been understood. Of 10 patients operated on, all but 1 were relieved of symptoms. The exceptional patient had only partial relief. Roentgenographic examinations of the patients who were not operated on confirmed the presence of cervical ribs when present, and the neurologic and vascular examinations elicited the same findings as in the patients who were operated on. All gave a history of traumatism. The symptoms under the heading of cervicobrachial syndrome may be classified as neurologic or vascular or a combination of the two. These classifications arise from and are an expression of the major pathologic changes in the disease. The causes are similar but the pathologic processes are different. Compression of nerve tissues produces numbness, pain, paralysis and loss of function; compression of vascular structures results in moderate pain, edema, swelling and obstruction of the blood flow, ending in clotting in the vessels and, if serious enough, death of the tissues supplied by these vessels. The location of the pathologic changes is confined to a small area, but one which is full of nerves and blood vessels, surrounded by muscles and osseous structures which have undergone great and vital changes in the course of evolution and embryonic development. Many of the diseases in this small region are the result of developmental defects. The theoretic etiologic factors of the cervicobrachial syndrome are: (1) compression of the nerve trunks, (2) injury to the nerve trunks, (3) injury to the sympathetic and the vasomotor nerves, (4) traumatism of the scalenus anterior muscle, (5) embryonic defect, (6) postural or functional defect, (7) narrowing of the upper thoracic cap as a result of adjacent infection or anatomic defect, (8) acute infection producing myositis and (9) intermittent traumatism to the subclavian artery. J. A. M. A.

ATYPICAL FACIAL NEURALGIA. MARK ALBERT GLASER, Arch. Int. Med. **65**:340 (Feb.) 1940.

Glaser believes that there exists a type of facial neuralgia transitional between migraine and trigeminal neuralgia which he designates as primary atypical facial neuralgia. It is characterized by pain which is always deep seated and aching, burning or throbbing in character. No specific factor could be held responsible for the onset of the pain, which in 33 per cent of the cases was bilateral. The distribution of pain was in a circular area within the distribution of the vascular supply of the face and head. It is frequently aggravated by such local factors as cold, heat, eating, worry, constipation and exertion. In 50 per cent of the cases of atypical neuralgia, sympathetic phenomena, such as lacrimation, blurred vision, unequal pupils, photophobia and corneal infection, are present. The patients, who are chiefly females, have continual annoying pain with superimposed severe exacerbations. There is an associated neurosis, which is believed to develop secondarily to the persistent annoying, irritating pain. Addiction to narcotics is not uncommon in association with atypical neuralgia, while it is rare with trigeminal neuralgia.

The author gives the following useful classification of atypical facial neuralgia.

I. Primary atypical facial neuralgia

II. Secondary atypical neuralgia due to various clinical entities
   1. Sphenopalatine and vidian neuralgia
   2. Postherpetic trigeminal neuralgia
   3. "Trigeminal ghosts"
   4. "Trigeminal ghosts" with lingual spasm
   5. Syndrome due to abnormalities of the mandibular joint
   6. Autonomic faciocephalalgia
   7. Painful convulsive tic
   8. Headache due to hypertonicity of muscles of the neck
   9. Senile neuralgia

III. Atypical facial neuralgia produced by systemic diseases
   1. Allergy
   2. Endocrine disturbance
   3. Psychoneurosis

IV. Atypical facial neuralgia due to lesions of the head, chest and abdomen
   1. Infections about the head
      (*a*) Mastoiditis
      (*b*) Thrombosis of the cavernous and longitudinal sinuses
      (*c*) Deep-seated facial abscess
   2. Tumors of the head and neck
   3. Intracranial lesions
   4. Dental sepsis
   5. Deviations and spurs of the nasal septum
   6. Ocular lesions
   7. Lesions of the chest
   8. Pathologic conditions in the abdomen and pelvis

The pain of atypical neuralgia is of a burning, pressing, aching, discomforting nature. It is not acutely lancinating, as in peripheral nerve neuralgia. The atypical neuralgia is not identical with the distribution of any cranial nerve, but does follow to a degree the course of the vasculature of the head.

In the treatment of atypical facial neuralgia every effort should be made to eliminate the secondary factors which may precipitate the pain. The best results are obtained in those cases in which the pain has been of short duration. Medical treatment consists of the use of the choline compounds, as well as epinephrine, ergotoxine, amyl nitrite, physostigmine and atropine. Resection or blocking the cervical sympathetic fibers has afforded relief in some cases, but it is strongly recommended that all medical measures be employed and exhausted before any operative procedure is carried out.

BECK, Buffalo.

ACHLORHYDRIC HYPOCHROMIC ANAEMIA ASSOCIATED WITH PERIPHERAL NEURITIS. C. WORSTER-DROUGHT and J. SHAFAR, Brit. M. J. **2**:273 (Aug. 5) 1939.

Worster-Drought and Shafar call attention to the fact that organic changes in the spinal cord and peripheral nerves occur rarely in idiopathic hypochromic anemia, in contrast to their frequent occurrence in pernicious anemia. A review of the literature divulges differences of opinion as to whether involvement of the nervous system occurs in association with hypochromic anemia.

Two cases of hypochromic anemia associated with objective neurologic signs, 1 in a patient 70 years of age and the other occurring as a sequel to gastrectomy, are reported. In both cases there was multiple neuritis associated with gastric dysfunction. The neuritis has been considered by Douthwaite as "dependent on an adequate supply of neuropoietin or some allied substance from the gastric or duodenal mucosa." Other authors have suggested that it may be the result of a vitamin B deficiency. The authors believe that in their cases there was an association between iron deficiency and neuritis because of the pronounced improvement of neurologic symptoms following iron medication.

ECHOLS, New Orleans.

CERVICAL RIBS. M. BELGRANO, Gior. ven. di sc. med. **14**:155 (March) 1940.

Belgrano studied 31 cases of cervical rib and 6 of hypertrophy of the transverse process of the fourth cervical vertebra. There were 30 female and 7 male patients. Trauma was the cause of symptoms in 6 cases. Vascular or neurologic manifestations were present in all but 6 cases. The most frequent symptoms were unilateral or bilateral pain in the shoulder and arm, frequently associated with muscular atrophy, nuchal pain, formication, paresthesias, variation in local temperature and other sensory, motor and vascular disturbances. Acute headache was the predominant symptom in 1 and cough in 5 cases. There were paresis of the dome of the diaphragm in 3 cases and paralysis of vocal cords in 1. The arterial blood pressure was diminished on the involved (or predominantly involved) side as compared with that on the normal side. The roentgenograms demonstrated the condition to be bilateral in 21 cases.

J. A. M. A.

POSTDIPHTHERITIC PARALYSIS. J. BULLÓ and H. CERASO, Rev. neurol. de Buenos Aires **4**:55, 1939.

A man aged 22 had severe sore throat; the clinical diagnosis of diphtheria was made and was confirmed bacteriologically. He was given a total of 55,000 units of antitoxin. A week later, there developed difficulty in phonation and deglutition, diplopia and flaccid, painful quadriplegia. The spinal fluid contained 6 cells per cubic millimeter and 0.65 per cent of albumin; the Wassermann reaction was negative. Of particular interest was a study of the fluid for diphtheria toxin and antitoxin; it contained none of either (that is, less than $\frac{1}{300}$ unit per cubic centimeter). At the same time, the blood contained $\frac{1}{30}$ unit per cubic centimeter. The patient made a gradual recovery.

PUTNAM, New York.

Cerebrospinal Fluid

THE CEREBROSPINAL FLUID IN ANTERIOR POLIOMYELITIS. J. C. DRURY and A. F. SLADDEN, Brit. M. J. **2**:557 (Sept. 9) 1939.

In 1938, Drury and Sladden subjected 55 specimens of cerebrospinal fluid taken from 53 persons suspected of having the disease to enumeration of cells, differential count and complete chemical analysis. Of these, 35 patients had definite cases of poliomyelitis, 3 probably a mild form, 4 an abortive form and 11 other diseases. In the proved cases of poliomyelitis the spinal fluid showed slight pleocytosis, a

slight increase in protein, the presence of globulin and a definite, though slight, Lange curve. This study demonstrates the diagnostic value of a detailed analysis of spinal fluid in suspected cases of poliomyelitis. ECHOLS, New Orleans.

ASCORBIC ACID IN CEREBROSPINAL FLUID. M. CASTEX and M. SCHTEINGART, Prensa méd. argent. **27**:905 (May 1) 1940.

Castex and Schteingart made quantitative determinations of the ascorbic acid content of the cerebrospinal fluid, either normal or altered from disease of the central nervous system, of 59 adults ranging in age from 16 to 70, and likewise the ascorbic acid content of the cerebrospinal fluid, blood and urine of 10 patients of this group. The amount of ascorbic acid averaged 0.0027 Gm. for each hundred cubic centimeters of normal cerebrospinal fluid, and 0.0021 Gm. for each hundred cubic centimeters of pathologic cerebrospinal fluid. The ascorbic acid values for the normal fluid were higher than those for the blood and the urine of the same patients and were independent of one another. There was no relationship between the age and the amount of ascorbic acid in the normal cerebrospinal fluid. The quantitative variations of ascorbic acid in the cerebrospinal fluid in diseases of the central nervous system were inconstant and were not related to the disease or to the alterations of the fluid. Simple quantitative determination of ascorbic acid in the cerebrospinal fluid is of no diagnostic value in determining hypovitaminosis C, as the figures may be normal in the presence of vitamin C inadequacy. The determination of ascorbic acid in the blood and urine after ingestion of vitamin C (administration of vitamin C for from eight to ten consecutive days, up to a total dose of from 0.3 to 0.5 Gm. of the substance) is a reliable clinical test for the diagnosis of hypovitaminosis C. J. A. M. A.

PASSING OF VITAMIN C INTO THE SPINAL FLUID IN CASES OF INJURY TO THE HEMATOENCEPHALIC BARRIER. MICHIO KASAHARA and ITSUO GAMMO, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:733 (Oct.) 1939.

In 17 adult male rabbits the spinal fluid was removed by cisternal puncture and the vitamin C content determined by titration with 2,6,dichlorphenolindophenol. One-half cubic centimeter of a 3 per cent suspension of aleuronat was then injected into each animal subdurally. From twenty-four hours to one week after these injections 0.1 Gm. of ascorbic acid was injected intravenously into each animal. One hour after the injection of ascorbic acid spinal fluid was withdrawn again and its vitamin C content determined. The results show that vitamin C passed more readily into the spinal fluid in animals with acute meningeal irritation. The amount of vitamin C is definitely less with more chronic irritation. Vitamin C passes more readily into the spinal fluid when the hematoencephalic barrier is damaged by experimental meningeal irritation. SAVITSKY, New York.

SPINAL FLUID IN THE DIFFERENTIAL DIAGNOSIS OF CEREBRAL ARTERIOSCLEROSIS. HEINRICH WEIGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:792 (Feb.) 1940.

Weigel studied the spinal fluid in 94 cases of cerebral arteriosclerosis. Simple arteriosclerosis refers to cerebral changes without massive destruction of brain tissue, the small areas of softening usually being at a distance from the ventricular system. The blood pressure in these cases was moderately elevated. There were 17 cases of this type (18 per cent). In half these cases the spinal fluid was normal; in the other half there was mild increase in the total protein content, which usually reached a high normal and never exceeded 70 mg. per hundred cubic centimeters. The globulin-albumin ratios were low, being between 0.05 and 0.15, and 0.29 in only 1 case. There was marked predominance of albumin.

Eleven cases of simple cerebral arteriosclerosis with other somatic complications, excluding syphilis, were studied. The complications were tuberculosis,

carcinoma, diabetes mellitus, pneumonia, erysipelas and alcoholic psychosis. In most of these cases there were no changes in the spinal fluid. In some instances there was a mild increase in the protein content. In only 1 case of erysipelas was there pleocytosis. Albumin was more increased than globulin. In neither this group nor in the preceding group were there any changes in the colloidal gold curves.

In 14 cases of cerebral arteriosclerosis with latent syphilis macroscopic examination of the brain showed only arteriosclerosis. In 3 cases there was mild atrophy of the frontal lobes, but no serologic or clinical evidence of dementia paralytica. The incidence of increase in protein was higher in this group; in 5 cases the values were above 50 mg. per hundred cubic centimeters, and in 3 cases 75 mg. or above. The globulin-albumin ratio was higher in this group. Globulin was increased as compared with the albumin. In almost all the cases there were abnormal colloidal fold curves of syphilitic type. The Wassermann reaction of the spinal fluid was positive in only 3 cases. The diagnosis of syphilis was made by positive serologic reactions of the blood in 10 cases, by the presence of syphilitic aortitis in 2 cases and at autopsy in the last 2 cases. Weigel believes that all the positive findings in the spinal fluid were due to syphilis of the nervous system, whether demonstrable pathologically or not. He does not accept the theory that these spinal fluid findings are due to lowering of the hematoencephalic barrier as a result of the syphilitic and arteriosclerotic process, allowing abnormal substances from the blood to enter the spinal fluid.

In 19 of 35 cases of arteriosclerosis with contracted kidney, Weigel found colloidal gold curves similar to those characteristic of latent syphilis. There was mild pleocytosis in 6 cases (12 to 43 cells per cubic millimeter). The total protein content was not elevated. In 4 cases it was 70 mg. per hundred cubic centimeters or over, with a maximum of 125 mg. in 1 case. The globulin-albumin ratios were all low. These changes are due to the passage of altered protein from the blood into the spinal fluid.

In 2 of 8 cases of pachymeningitis with cerebral arteriosclerosis there was a mild increase in protein, as described in instances of so-called simple arteriosclerosis. In the other cases there were xanthochromia, increase in protein and, in a few cases, pleocytosis. The colloidal gold curves were positive in these cases. In 5 cases in which there were massive cerebral damage and foci of softening near the ventricle the findings were as described in the pachymeningitis group. In 1 case there was blood in the spinal fluid. In 4 cases in which cardiac decompensation was present there were no cells, but protein, especially albumin, was increased. There were changes in the colloidal gold curves, which were probably due to stasis.

SAVITSKY, New York.

NONPROTEIN NITROGEN CONTENT OF THE CEREBROSPINAL FLUID. WOLFRAM KURTH, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:459 (April) 1940.

Kurth examined 172 specimens of spinal fluid from 146 patients for nonprotein nitrogen values; 104 of the patients had organic disease of the nervous system. Conditions other than organic disease of the nervous system (vasomotor disorders, migraine or hysteria) were present in 42 cases. Halpern found the normal range of nonprotein nitrogen in the spinal fluid to be from 12.54 to 17.8 mg. and Brun from 11 to 19 mg. per hundred cubic centimeters. The lowest value in this series was 5.6 mg., in a case of trauma to the head, and the highest 67.2 mg., in a case of cerebral arteriosclerosis. Very high figures, such as are encountered with disease of the kidneys were found by Halpern in cases of acute meningitis (163.61 mg. per hundred cubic centimeters). There was no case of acute meningitis in this series. There was no difference between the nonprotein nitrogen content in idiopathic and that in symptomatic epilepsy. No correlation was found between the presence or absence of high values for nonprotein nitrogen in the spinal fluid

and the presence of organic disease of the nervous system. A normal nonprotein nitrogen value is not against the diagnosis of organic disease of the nervous system. No constant relation could be demonstrated between the total protein and the nonprotein nitrogen content. The nonprotein nitrogen values do not change with repeated lumbar or suboccipital punctures.

SAVITSKY, New York.

Muscular System

ELECTROCARDIOGRAPHIC AND SERUM POTASSIUM CHANGES IN FAMILIAL PERIODIC PARALYSIS. HAROLD J. STEWART, J. JAMES SMITH and ADE T. MILHORAT, Am. J. M. Sc. **199**:789 (June) 1940.

Stewart, Smith and Milhorat studied the serial changes in the electrocardiograms of a patient suffering from familial periodic paralysis during an attack, when the serum potassium was low. A white laborer aged 19 was brought to the hospital because of paralysis of three days' duration; speech had developed a peculiar quality, and swallowing was difficult. The chief finding on physical examination was flaccidity of the muscles below the neck. The only voluntary movement which the patient could make below the level of the neck was a slight motion of the thumbs and index fingers. A coarse systolic murmur was heard over the whole precordium, and the second sound in the mitral area was reduplicated. There was complete absence of all reflexes, except those of the pupils and jaw. A series of three records were made during the attack of paralysis: the first immediately on admission, the second and third eighty-five and one hundred and ten minutes, respectively, after administration of potassium chloride and the fourth the morning after the recovery from paralysis; another, taken four months later, was an additional control. The serum potassium level was 11 mg. per hundred cubic centimeters, only 50 per cent of the normal. When recovery was complete, however, it was 25.3 mg. per hundred cubic centimeters, a value within the normal range. The most striking changes and those responsible for the bizarre form of the electrocardiogram were prolongation of the PR, QRS and QT intervals, alteration in the form of the RT segment and decrease in amplitude of the T waves. The authors believe that the electrocardiographic changes are associated with the reduction in serum potassium.

MICHAELS, Boston.

CONGENITAL MYOTONIA IN THE GOAT. G. L. BROWN and A. M. HARVEY, Brain **62**:341, 1939.

Brown and Harvey studied a group of goats suffering from a form of congenital myotonia similar to Thomsen's disease in man. The animals appear normal when feeding quietly, but sudden exertion of any kind produces a myotonic seizure. When startled, all muscles of the limbs are rigidly contracted, the limbs become immobilized and the animal falls. The myotonia is worse after rest and tends to disappear after moderate activity. Experiments were carried out to determine the nature of the myotonia, whether contraction or contracture, as well as the location of the abnormality, whether central or peripheral. By means of a needle electrode it was ascertained that the myotonic muscle is in a state of incessant oscillatory electrical activity. Tapping the muscle, or even stroking the skin, evokes a burst of electrical impulses. The character, size and frequency of the impulses suggest that they are the responses of individual muscle fibers. This activity is not altered by section and degeneration of the motor nerve, nor is it affected by large doses of curarine.

Myographic studies show that stimulation of the motor nerve with a single volley produces a twitch response which differs from the normal chiefly in its delay in relaxation. Stimulation at low frequencies, however, results in a decrease in this phenomenon, and as stimulation is continued the response may approach

that of a normal muscle. The delay in relaxation is accompanied by oscillatory action potentials, and after a brief period of high frequency tetanus the after-discharge may be long lasting. The marked delay in relaxation after a short period of tetanus and its disappearance after repeated slow stimuli form a close parallel to the changes observed in the intact animal under voluntary movement, with sudden exertion or mild activity.

Intra-arterial injection of acetylcholine in the myotonic animals fails to reveal any abnormality in sensitivity to this substance. The contraction produced, however, is prolonged. The myotonic muscle also shows normal sensitivity to physostigmine. On the other hand, the muscles are extremely sensitive to small amounts of potassium chloride. Intra-arterial injection of this substance in doses insufficient to elicit a response in the normal goat produces a strong contraction associated with irregular action potentials in the myotonic animal. The myotonia and the mechanical and electrical sensitivity to tapping the muscle may be markedly reduced by the administration of quinine.

From these experiments it is concluded that the myotonic response, being accompanied by oscillatory action potentials, is a true muscle contraction and not a contracture. The fact that this electrical activity is unaltered by nerve degeneration or curarization is evidence that the abnormality is in the muscle itself. Although abnormalities of the central nervous system may exist, the disturbances in the muscle are sufficient to account for the symptoms observed. The essential abnormality appears to be a tendency of the muscle fibers to respond repetitively to any form of stimulation. This abnormality is in the muscle fiber itself, and does not involve the neuromuscular transmitting apparatus.

MASLAND, Philadelphia.

THE RELATIONSHIP BETWEEN AMYOTONIA CONGENITA AND CONGENITAL MYOPATHY. J. W. ALDREN TURNER, Brain **63**:163, 1940.

Turner describes a family of 13 children, 6 of whom suffered from amyotonia congenita. No other members of the family were affected.

The condition was present at birth, and probably before, as the mother could tell from the lack of fetal movements that the later children would prove to be affected. The picture was similar in all 6 patients. At birth, the infants were extremely hypotonic, and the limbs could be moved freely into abnormal postures. The muscles were flabby but not atrophied. Reflexes were absent. Voluntary movement was impossible. Strength gradually increased, reflexes appeared and hypotonia diminished, and by the age of 4 or 5 years the children could walk with a waddling gait.

The hypotonia diminished in adult life, and strength was sufficient to permit moderately strenuous pursuits. However, it was observed that at about the age of 6 localized wasting of the sternocleidomastoid, pectoral, trapezius and triceps muscles had developed in all the children, with slight atrophy of the serratus magnus, the spinati, the latissimus dorsi and the deltoid muscles. There was no localized atrophy of the legs, but 3 of the 4 patients who survived walked with a waddling gait. The atrophy was not progressive.

The transition of this condition from a state of amyotonia and marked flaccidity to one of myopathy with localized muscular atrophy marks the disease as a congenital myopathy. In further support of the myopathic basis of this form of amyotonia congenita is the fact that it is familial, that cases of amyotonia congenita and muscular dystrophy have been reported in the same family and that a few cases of muscular dystrophy appearing at birth have been observed.

Against this opinion are the facts that flaccidity is unusual in the myopathies and wasting rare in amyotonia. The transitional state in the cases described tends to negate this objection. A more serious objection is the fact that the myopathies are usually, but not always, progressive, and that any return of the tendon reflexes, such as was observed in these cases of amyotonia, is rare.

Although no pathologic studies are reported, it is believed that the condition here described differs from those of amyotonia congenita, which is related to Werdnig-Hoffmann disease and in which the anterior horn cells are affected. Although the prognosis differs greatly, clinical differentiation of the two conditions is difficult. The conclusion must be reached that amyotonia congenita is a symptom rather than a disease, and that it may be caused either by a congenital myopathy, as in the family reported here, or by a spinal disorder bearing a close relation to Werdnig-Hoffmann disease.

MASLAND, Philadelphia.

THE ROLE OF POTASSIUM IN MYASTHENIA GRAVIS. J. N. CUMINGS, J. Neurol. & Psychiat. **3**:115 (April) 1940.

In a previous report, Cumings demonstrated that the affected muscles in cases of myasthenia gravis contain more potassium than normal muscles and that administration of prostigmine to myasthenic patients was followed by a fall in muscle potassium and by a corresponding rise in serum potassium. In order to investigate the fate of the potassium leaving the muscles, Cumings administered a diet of a known potassium content to 2 patients with severe myasthenia gravis and determined the amount of potassium excreted in the urine and stools before and after injection of prostigmine, as well as after administration of an additional 3 Gm. of potassium followed by another injection of prostigmine. He found that, in spite of the increase in serum potassium, there was no increase in excretion of potassium or of inorganic phosphates in the urine and stools after the injection of prostigmine. A considerable increase in the excretion of potassium occurred only when the potassium was later added to the diet, but this was again unaffected by subsequent injection of prostigmine. The increase in the serum potassium following injection of prostigmine was associated with marked clinical improvement. By determining simultaneously the concentrations of potassium in the blood and muscle in another patient during varying intervals after the administration of prostigmine, it was found that as the blood potassium increased the muscle potassium fell, and that about two hours later when the muscle potassium rose the serum potassium fell, with corresponding relapse of the patient's symptoms. Thus, the potassium liberated from the muscles into the blood remains there for a time and then returns to the muscles, and the degree of muscular weakness is directly associated with the amount of potassium present in the muscle at any given time.

MALAMUD, Ann Arbor, Mich.

Special Senses

PLEXIFORM NEUROFIBROMATOSIS (RECKLINGHAUSEN'S DISEASE) OF ORBIT AND GLOBE, WITH ASSOCIATED GLIOMA OF THE OPTIC NERVE AND BRAIN. F. A. DAVIS, Arch. Ophth. **22**:761 (Nov.) 1939.

Plexiform neurofibromatosis of the eyelid and the region about the orbit and temple is a well recognized, though rare, manifestation of Recklinghausen's disease, usually appearing in early childhood. Other peripheral changes, such as cutaneous coffee-colored spots, molluscum fibrosum and multiple tumors of the peripheral nerves, are frequently present. The disease is recognized by the presence of a thickened, pendulous upper lid, which is often accompanied by a tumor-like mass in the temple, orbit and side of the face. These masses are soft and when palpated have the feel of knotted cords. When the nerves of the orbit are involved there is usually some degree of proptosis, and at times pulsation of the globe. Intraocular involvement also occurs, though it is rare.

Davis reports 2 cases of plexiform neurofibromatosis of the orbit and globe, with an associated tumor of the optic nerve. In addition, there was extensive intraocular neurofibromatosis. These intraocular changes resulted in buphthalmos.

The relationship of the tumor of the optic nerve to the condition is uncommon. Buphthalmos, however, is even more rare. Davis believes that the marked thickening of the choroid and the ciliary body, producing anterior displacement of the uveal tract, and subsequent adhesions of the root of the iris to the posterior surface of the cornea were the mechanical changes responsible for the development of increased ocular tension. In this case these adhesions were apparently augmented by the newly formed tissue incident to the neurofibromatosis, or proliferation of the ciliary nerves, in this region.

SPAETH, Philadelphia.

CLINICAL DETECTION OF EARLY CHANGES IN THE VISUAL FIELD. H. M. TRAQUAIR, Arch. Ophth. **22**:947 (Dec.) 1939.

As a rule it is only when defects of the visual field develop slowly that their initial stages can be examined. Study of the methods for the detection of early changes is therefore confined to conditions in which the onset is gradual, such as pressure from a tumor, chronic toxic amblyopia and chronic glaucoma, and is best undertaken with eyes in which the presence of defects is suspected although visual symptoms have not been noticed by the patient. The apparently normal field in cases of supposedly unilateral glaucoma or toxic amblyopia and the fields in cases of enlargement of the pituitary body in which there are no visual symptoms afford suitable material for investigation.

These incipient changes can be elicited only by weak stimuli, such as are capable of disclosing slight lowering of visual function in the affected area. In this connection two questions arise: First, what are the best and most practical methods of obtaining suitable stimuli? Second, in what part of the field are the earliest signs of functional impairment most likely to be capable of demonstration? A weak stimulus may be obtained in various ways. Of these the most generally useful is that of reducing the visual angle subtended by the test object by increasing its distance from the eye and diminishing its diameter. Other methods, such as altering the color of the test object or lowering the illumination under which the examination is conducted, are valuable under certain circumstances and may be used in conjunction with reduction of the visual angle.

Examples of early stages of slowly advancing defects are manifested in the curve scotomas of glaucoma, which commence as an outgrowth in the blindspot. Another condition is toxic amblyopia, which presents slowly developing defects in which early changes may be studied. Here, also, enlargement of the blindspot is commonly stated to be the initial factor. A scotoma is sometimes said to arise as an outgrowth of a blindspot in the shape of an index finger pointing toward the fixation area. In cases of tabetic optic atrophy, changes in the visual fields of various kinds develop slowly. Central vision may be normal, and the optic disk may show a healthy color, though commencing changes can be seen in the fields. Two well known types are the concentric contraction and the sector contraction. Slowly advancing changes in the fields of vision also are produced by pressure from the tumor. This may affect any part of the visual pathway. In the case of the optic nerve itself, a tumor may grow from a sheath or may arise from the orbit apart from the nerve. Here, again, it will be found that although the pressure affects the nerve, presumably first the periphery, it is the more central regions of the fields which are first affected. At the distal end of the nerve the papillomacular bundle is superficial, and a peripheral lesion here may produce peripheral contraction of the fields together with centrocecal scotoma. Disseminated sclerosis may show rapid development of a junction scotoma, that is, a unilateral temporal hemianopic or quadrantic central scotoma, indicating the site of the lesion at the junction of the optic nerve and the chiasm. In so far as the chiasm is concerned, one is on firm ground in localization of these early changes. This includes bitemporal hemianopia, which, while common, is equally rarely symmetric in the earlier stages. In fact, it is common to find defects so minimal at this time that it would be difficult to say whether a homonymous or a bitemporal

hemianopia will ultimately develop. A similar principle applies to suprachiasmal pathologic changes. Early changes here are likely to be found in deflection of the internal rather than of the peripheral isopters of the field. The early failure of the central part of the field, whether in the form of slight depression or of true central scotoma, also is not uncommon. It is probably due to disturbances of the blood vessels as a visual nerve path, so that it is nutritive in character.

SPAETH, Philadelphia.

VISUAL HALLUCINATIONS AND THEIR NEURO-OPTICAL CORRELATES. L. M. WEINBERGER and F. C. GRANT, Arch. Ophth. **23**:166 (Jan.) 1940.

Weinberger and Grant state that evidence can be adduced to show that hallucinations of vision occur from lesions at every physiologic level of the neuro-optic apparatus. This concept is apparently at variance with the ideas now current in neurologic circles respecting the clinical significance of visual hallucinations. Hallucinations do not necessarily appear only in the hemianopic fields, and the complexity of the hallucinations has no localizing value in the diagnosis of focal lesions of the nervous system. The authors report 16 cases of tumor implicating only the optic nerves or chiasm. All the patients had visual hallucinations of one kind or another.

The authors conclude: (1) visual hallucinations in themselves have no localizing value whatever in focal diagnosis; (2) visual hallucinations may be provoked by lesions at any level of the neuro-optic apparatus; (3) visual hallucinations are not due to local cortical excitability but are psychologic phenomena, involving the total integrative activities of the mind; (4) the complexity of the images depends on psychologic and constitutional factors and not on cortical psychic organization; (5) there is no constant relation between the portion of the field into which the hallucinations are projeced and the objectively blind areas.

SPAETH, Philadelphia.

ROLE OF THE CERVICAL SYMPATHETIC NERVE IN THE LIGHT REFLEX OF THE PUPIL. E. A. SPIEGEL and N. P. SCALA, Arch. Ophth. **23**:371 (Feb.) 1940.

The Hering-Sherrington law of reciprocal innervation of antagonists has been found valid not only in the innervation of striated muscles but also in the innervation of some parts of the autonomic nervous system. Dilatation of the pupil can occur not only by stimulation of the dilator but also by innervation of the antagonist, the sphincter, of the pupil. Because of this, Spiegel and Scala attempted to answer the question whether the law of reciprocal innervation is valid for the light reflex.

Cats were employed for the experiment. The right oculomotor nerve was cut at the base of the brain. Physostigmine salicylate was then instilled, after careful measurements of the pupil, and at certain definite intervals the size of the pupil and the presence or absence of the light reflex were determined. These experiments showed that after illumination of the sphincter muscle there was no indication of a reaction of the dilator muscle to illumination or darkness, even if a medium width of the pupil was restored by instillation of physostigmine salicylate. The authors infer that the part played by the cervical sympathetic nerve in dilatation of the pupil in the dark is not due to increase of the impulses transmitted by this nerve in the dark, but simply to the tonic innervation of the dilator muscle, which is not influenced by changes in illumination of the retina. They further confirmed this conclusion by a set of experiments in which the electrical potentials of the cervical sympathetic nerve of cats were recorded.

Spiegel and Scala conclude that the cervical sympathetic nerve slightly impairs the ability of the pupil to dilate in the dark; that instillation of benzedrine sulfate in the conjunctival sac of an eye in which the dilator muscle is paralyzed by cervical sympathectomy may transitorily abolish the slight impairment of the pupil to dilate in the dark; further, that after section of the ocular nerve changes

in the diameter of the pupil in the light and in the dark could not be noticed, even when a medium width of the pupil was restored by instillation of physostigmine salicylate. Electrosympatheticograms demonstrated that the cervical sympathetic nerve participates in the light reflex of the pupil only in that its continuous impulses maintain a tonic contraction of the dilator muscles, enhancing the effect of the relaxation of the sphincter in the dark. There is, however, no definite increase in excitation of the nerves.

The authors believe that in view of these experiments the pathologic phases of the Argyll Robertson pupil should be sought not in impairment of the dilator innervation, but of the reflex apparatus inducing contraction of the sphincter muscle.

SPAETH, Philadelphia.

PARALYSIS OF DIVERGENCE. M. B. BENDER and N. SAVITSKY, Arch. Ophth. **23**:1046 (May) 1940.

This article again brings to the front the problem whether divergence is merely a relaxation of convergence or whether it exists as an active function in which contraction of the external rectus muscles is accompanied by simultaneous concomitant relaxation of the two internal rectus muscles. If this is so, the acts of convergence and divergence and the mechanisms through which these two functions are achieved must be antagonistic and reciprocal in their action. The center for convergence undoubtedly lies in Perlia's nucleus. Whether a center for divergence exists in or about that region of the midbrain has not been clearly demonstrated. Clinically, however, one can conclude that paralysis of divergence does occur as a definite pathologic entity, and therefore one must presuppose the presence of a divergence center.

Bender and Savitsky report the case of a girl aged 18 who entered the hospital because of headaches and double vision. The double vision was homonymous and less evident at the near point, and did not increase when the eyes and the test objects were moved to either side. The fields of vision and the ocular movements were normal. There were no evidences of ocular palsy, though at times there seemed to be transient internal strabismus in each eye. Lumbar puncture revealed an initial pressure of 200 mm. of water. The spinal fluid was clear and colorless; the serologic reaction was negative; the sugar and protein contents were normal, and there were 4 cells per cubic millimeter of fluid.

Two years after her first admission to the hospital the patient was readmitted because of bilateral papilledema. The fields of vision were normal, but the blind-spots were enlarged. Slight internal strabismus was present in the left eye, but there was no weakness of abduction in either eye. A roentgenogram revealed symmetric internal hydrocephalus. Exploratory craniotomy was followed shortly by the patient's death. Autopsy revealed a cavernous hemangioma lying about and occluding the aqueduct of Sylvius. There was marked enlargement of the ventricular system anterior to the aqueduct, in the presence of an undilated fourth ventricle. Microscopically, many of the ganglion cells in the nuclei of the third and fourth cranial nerves showed degenerative changes, characterized by eccentricity, swelling and blurring of the nuclei. The nucleus of the abducens nerve was normal on both sides.

From these pathologic observations, therefore, it appears that divergence can be caused by disease about the aqueduct with resulting degenerative changes in the nuclei of that region, even though the nucleus of the abducens nerve itself may be normal.

SPAETH, Philadelphia.

RARE CAUSES OF COMPRESSION OF THE INTRACRANIAL PORTION OF THE OPTIC NERVE. G. P. SOURDILLE and M. DAVID, Ann. d'ocul. **176**:756 (Oct.) 1939.

Sourdille and David report the case of a patient with ocular symptoms characteristic of an optochiasmatic attack and auditory signs of an acoustic neurinoma. Operation revealed slight swelling of the optic nerve and the presence of a very

large median ventricle. Subsequent craniectomy in the posterior fossa revealed an acoustic neurinoma. In another case reported by the authors, primary bilateral optic atrophy was revealed at autopsy to be due to compression of the optic nerve by an atheromatous plaque at the bifurcation of the carotid artery.

BERENS, New York.

Cerebellum and Brain Stem

TUMORS OF THE MEDULLA OBLONGATA, PONS AND MESENCEPHALON. O. FOERSTER and O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:295 (Jan.) 1940.

Foerster and Gagel report on 13 more cases of tumors of the brain stem, all histologically verified. In this series are included 2 cases of spongioblastoma polare, 1 of ganglioglioma, 6 of malignant glioblastoma, 1 of medulloblastoma, 2 of metastatic carcinoma and 1 of astrocytoma.

In the first case of spongioblastoma polare the tumor involved the right side of the medulla in a man aged 58, who died after an abdominal exploration which gave negative results. No neurologic examination was made. There was a history of vomiting for four months. After the operation the patient became restless and disoriented. The second case was that of a boy aged 17 who had shown mental symptoms for about a year before admission. He was restless and querulous, and at times was euphoric and showed manic-like behavior. For about a month before admission he complained of headache and vomiting. On admission he presented a syndrome of a lesion of the quadrigeminal plate, with supranuclear conjugate paresis of upward gaze, marked nerve deafness with intact vestibular responses and anisocoria, with pupils which were fixed to light and in convergence. There were, in addition, marked disturbance in equilibrium, with a tendency to fall to the left, left spastic hemiparesis and impairment of spinothalamic modalities on the left side. A cystic tumor was found at operation in the region of the corpora quadrigemina. After operation there was transitory improvement. The patient later experienced sensory and motor changes on both sides of the body and cerebellar fits. A spongioblastoma polare was found in the form of a cystic tumor destroying the tegmen of the peduncle and the anterior portion of the pons.

The only case of ganglioglioma was that of a boy aged 3, whose presenting symptom was weakness in the right lower limb. About one-half year later weakness in the right arm was noted. About one month after the onset there was transitory pain in the left temple. There was no vomiting. The clinical picture was that of progressive right hemiplegia, and finally tetraplegia. None of the cranial nerves seemed to be affected in spite of extensive involvement of the brain stem. The duration of the illness was about three and one-half years. A ganglioglioma myelinicum involved mainly the ventral side of the bulb, pons and peduncle. Two similar tumors have been previously reported by the authors.

Of the 6 glioblastomas, 5 involved the pons and medulla and 1 the quadrigeminal region. The average age of the patients was 23 years, the oldest being 63 and the youngest 6. The average duration was twelve months, the shortest being one month and the longest two years and eight months. Three of the patients were males and 3 females. Three of the glioblastomas were of the microcellular and 3 of the multiform variety. In 2 of the cases there were no changes in the eyegrounds after a duration of symptoms of six and five months, respectively. In a third case mild dilatation of the veins appeared after six months; in a fourth, choking of the disks came on after two years and eight months. In the other 2 cases papilledema was noted early during the course of the illness.

In 5 of the 6 cases of glioblastoma there was definite evidence of paresis of conjugate gaze, either lateral or upward. In only 1 of the cases was there typical hemiplegia cruciata, with involvement of the right seventh and fifth nerves and contralateral hemiplegia with sensory changes. In 1 of the cases the only evidence of involvement of the cranial nerves was bilateral paralysis of the abducens without

papilledema. Involvement of the nucleus of the eighth nerve was encountered in 1 case, with normal vestibular responses on the affected side. Palatoplegia was noted in 1 case, without laryngoplegia. Persistent singultus was observed in only 1 case. This was the only instance of hiccup in the whole series of cases of tumor of the brain stem. Mahoney found this symptom in only 2 of 72 cases reported in the literature.

The case of medulloblastoma in this series is the only instance of an intrapontile tumor of this type known to the authors. The patient was a girl aged 5. The illness was of three months' duration. Soon after a fall down some steps, paralysis of the left sixth nerve and progressive weakness of the right side of the body appeared. There was also impairment of the motor and sensory portions of the left fifth nerve. There was no papilledema.

Bulbopontile metastatic carcinomas are rare, Mahoney having found only 1 in 53 cases of verified tumors in this region reported in the literature. The first case in the present series was in a woman aged 53 with sudden onset of hemiplegia involving the left side about four years after mastectomy for carcinoma. After some improvement, about five months later, there was another apoplectic episode. In addition to left spastic hemiparesis with homolateral sensory changes, paralysis of the right sixth nerve appeared. There were bilateral paresis of conjugate gaze, dysarthria and absence of reaction of the pupils to light and in convergence. The symptoms were due to an intrapontile tumor, with hemorrhage into it, which extended to the level of the trochlear nucleus. The symptoms were of seven months' duration. The second case of intrapontile metastatic carcinoma was that of a man aged 46, with an unknown primary focus. Soon after a blow behind the left ear he began to complain of double vision, dizziness, vomiting and dysphagia. The positive findings on admission were left hemiparesis, with homolateral hemianesthesia, left corneal areflexia, palatoparesis on the left, dysarthria, vertical and lateral nystagmus and inconstant mild involvement of the left sixth nerve. The absence of vestibular reactions on one side with intact cochlear function was noted as an unusual type of dissociation. A markedly defective corneal reflex with otherwise intact function of the trigeminal nerve is unusual in cases of intrapontile lesions. The dysarthria, dysphagia and laryngoplegia were considered as supranuclear (pontile pseudobulbar palsy).

The only case of astrocytoma on the left side of the pons was that of a girl aged 5. The illness began immediately after a fall and injury to the back of the head. The child seemed to fall to the left soon after the blow on the head. Pains in the back of the head soon appeared. The next day weakness of the right hand appeared, and two days later weakness in the right leg was noted. On admission, eight days after the onset, typical alternating hemiplegia was noted, with paralysis of the sixth and fifth nerves on the left and right spastic hemiparesis; there were complete paralysis of conjugate lateral gaze to the left and lateral and vertical nystagmus. The dissociation between anarthria and dysphagia was considered unusual. Ptosis on the right side, mydriasis and a sluggish pupil on the right were probably neighborhood phenomena relative to the peduncle (edema?). The duration in this case, seven weeks, was unusually short. The average duration of symptoms in 12 cases of previously reported intrapontile astrocytomas was three years and three months. SAVITSKY, New York.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

LAUREN H. SMITH, M.D., *President, in the Chair*

Regular Meeting, May 10, 1940

Histamine Desensitization of Allergic Epileptic Patients. DR. JOSEPH A. BEAUCHEMIN, Middletown, Conn. (by invitation).

For some years it has been noted that epileptic patients occasionally had seizures after light as well as heavy meals. The repeated and frequent eating of specific foods, especially meats, seemed to cause an increase in the number and severity of the attacks. Over a period of two years, 100 patients with chronic epilepsy and psychosis were systematically tested with allergens of the food, bacterial and plant and weed pollen classes.

The reactions obtained gave proof of a definite hyperallergic constitution in almost 50 per cent of the patients. They also exhibited reactions common to them as a group, as compared with a much larger number of control patients. Three patients with acute epilepsy who were not psychotic gave similar reactions during the same period.

Routine of Examination.—1. Family History: An attempt was made to trace back through two generations of ascendants and collaterals any occurrence of epilepsy, migraine, hay fever, food idiosyncrasies, urticarias, cutaneous lesions or other possible hyperallergic manifestations. At least 60 per cent of the patients with chronic epilepsy showed a positive family history for one or more of these conditions, and the 3 patients with the acute form all gave a family history of allergy.

2. Personal History: The same search for a hyperallergic symptomatology was pursued in the patient's own history.

3. Hypersensitivity Tests: The patients were tested with the allergens by the skin scratch, the intradermal and occasionally the electrophoretic method. The Vaughan test was also used.

Of a total of 103 patients, 65 were shown to have a hyperallergic constitution. While this was not thought to be the causative factor in the production of epilepsy in these cases, desensitization with the basic, nonspecific heteroprotein histamine was attempted.

A series of thirty injections was given the patients, one every other day, by the subcutaneous route. The dose was graduated from 0.00001 to 0.01 mg. of histamine phosphate. Mild exaggeration of the mental symptoms, an increase in the number or severity of the attacks and even status epilepticus in a few cases were noted during the injections.

After the cessation of the treatments, improvement in the condition of some of the patients was noted. All 3 nonpsychotic patients with acute epilepsy showed a marked reduction in the number and the severity of the seizures. One of these is entirely free of attacks; another has only one monthly, mild "petit mal" manifestation. Of those with chronic epilepsy, a patient who for years had experienced ten to forty "grand mal" convulsions per month has been entirely free of any seizure for over two years. There has been a marked reduction in the number of seizures, as well as in their severity, in the case of 6 other psychotic patients suffering from the chronic form of this disease. It is my opinion that this treatment might well be of real benefit in selected cases of chronic epilepsy and in cases of acute epilepsy of short duration without psychosis.

Histaminase and Epilepsy. Dr. E. D. Chankin (by invitation).

It has been noted in the literature that approximately 50 per cent of epileptic patients show allergic tendencies. According to the present theory such tendencies are based on the presence of unresolved histamine in the body tissues, and it would seem that some substance capable of inactivating histamine should be of value. Such a substance, histaminase, presumably an enzyme, is claimed to have been found in certain of the body tissues, particularly the kidneys, small intestine, liver and adrenal glands. On the basis of these theoretic considerations and the reported work of Dr. Joseph A. Beauchemin, a group of 11 patients was selected. The duration of their illness ranged from nine to twenty-eight years. The persons selected were known epileptic patients whose care has presented special problems. Previous treatment had failed to bring about cessation of their seizures or to prevent deterioration. It was therefore felt that if any improvement occurred in this group it would be attributable to the histaminase.

No change was made in their previous diet, medication or surroundings, other than the administration of the histaminase. The treatment was started with a dose of 10 units three times a day. Symptoms such as headache, flushing, nausea, vertigo and visual disturbances, which are said to be evidence of intolerance to the drug, were watched for, but as yet have not been noted.

The patients have been kept under close observation. A specially prepared chart has been used on which pulse rate, blood pressure, weight and results of ordinary laboratory studies are recorded periodically. The chart permits daily record of the patient's behavior, with particular reference to the following symptoms: destructiveness, assaultiveness, noisiness, profanity, irritability, impulsiveness, suggestibility, confusion, excretory habits, sexual behavior and occupational adjustment. These are graded as mild, moderate and marked. Convulsive attacks are charted with reference to type, frequency, time of day and day of month.

An attempt has been made to compare the results of this histaminase treatment to date with the records available of the condition and behavior of the patients prior to this treatment. Up to the present, no essential change has been noted in the number, type or severity of seizures or in the behavior and adjustment of the patients. It is interesting to note that in 1 patient there has apparently been a reversal in the ratio of day and night seizures. With regard to the effect of the drug, no significant change in pulse, temperature, blood pressure, weight or ordinary laboratory findings has been noted. As already mentioned, no evidence of intolerance has yet appeared.

In conclusion, a preliminary report has been presented on the results of forty days' treatment with histaminase of 11 epileptic patients. The period of observation has been too short and the number of cases too few for definite conclusions, but the indications are that patients with chronic epilepsy benefit little or not at all.

DISCUSSION ON PAPERS BY DRS. BEAUCHEMIN AND CHANKIN

Dr. F. H. Lewy: Dr. Beauchemin's observations are interesting. As he himself has stated, they have to be checked on a larger material. Suppose that such a check confirms the present investigation. Two questions have to be asked: 1. What is the relation between allergy and epilepsy? 2. What is the relation between the histamine or histaminase treatment and the improvement of the epileptic condition? With respect to the first question: According to statistics based on a large number of cases, in not more than about 2 per cent of adult epileptic patients has it been possible to prove that allergy played a major role in the production of seizures. This statement leads directly to the question: What phenomena should be considered as unequivocal proof of the causal relation of allergic constitution and physical manifestations, such as urticaria, hay fever or, in the present case, epileptic convulsions? According to an editorial in *The Journal of the American Medical Association* (**106**:1988 [June 6] 1936), neither allergic skin tests nor the Vaughan test should be considered as furnishing such unequivocal proof of allergic constitution. The only reliable test is seen in the fact that forcing a certain substance, such as milk, increases allergic attacks while eliminating it

from the diet decreases the attacks. On the basis of this accepted criterion, 10 per cent of the whole population of the United States show manifest signs of allergy and an additional 40 per cent general allergic signs. This 50 per cent corresponds exactly with the occurrence of positive cutaneous reactions among the author's epileptic patients. In other words, one may take it for granted that a constitutional condition which appears to be present in every second American will also be found in every second epileptic patient; that, after all, confirms the author's premise, whether or not the professional allergists accept his method of examination.

Much more difficult is a discussion of the results of specific or nonspecific desensitization with histamine or histaminase. The results of dermatologists with the latter drug are not favorable, as evidenced in a paper by Miller and Piness (Potassium Salts in Hay Fever, *J. A. M. A.* **114**:1627 [April 27] 1940), who in not one of 42 cases of urticaria found satisfactory proof of any effect of treatment with histaminase. Desensitization with increasing doses of histamine, on the other hand, is doubtless effective in some cases, although a good result in less than 14 per cent of 65 patients may statistically be entirely within the range of chance. Yet the marked improvement of 9 of 69 patients over a longer period seems to me encouraging enough to justify continuing these studies in the hope of detecting the peculiarities of those patients, who, in fact, did react favorably to this treatment.

DR. HAROLD D. PALMER: Was there any depression in gastric acidity during the histaminase therapy? In our study of the problem of migraine headache, my associates and I have investigated the allergic phenomena which are so often associated with migraine, and as part of that study we have given histaminase in doses of from 30 to 100 units daily. In a number of the cases there was a troublesome reduction in gastric acidity with accompanying gastric symptoms, which were distressing to the patient. In order to continue the study of histaminase in these cases it was necessary to administer diluted hydrochloric acid by mouth. This controlled the symptoms and apparently did not interfere in any way with the tissue effects of the histaminase.

DR. JOSEPH A. BEAUCHEMIN: No such symptoms occurred in any of the patients in this study. Of course, these patients are psychotic, and there is little one can expect to obtain by questioning them, the only alternative being careful observation.

DR. HAROLD D. PALMER: Was there any diarrhea?

DR. JOSEPH A. BEAUCHEMIN: None. No untoward symptoms were noted in the patients. What was the dose given your patients, Dr. Palmer?

DR. HAROLD D. PALMER: Thirty to 100 units (6 to 20 tablets) daily, by mouth.

DR. MELVIN W. THORNER: It seems to me that this question of the relationships of epilepsy is an extremely important one. Practically all one knows of epilepsy is that it is some sort of trick mechanism which may be set off. Possibly allergy is one of the agents which may set off such a mechanism. I think that at the present stage it is probably not quite logical to attribute any causal relation to epilepsy. It is known that certain psychologic states can set off an epileptic attack and that other things are capable of so doing. These are regarded only as trick mechanisms rather than as essential factors in the epileptic type of neurologic organization. As Dr. Palmer and others have pointed out in various cases, some of the conditions which seem definitely linked with allergy have been shown, on closer inspection of the statistics, to present bases for doubt of the existence of such links: for instance, the supposed relation between migraine and allergy and that between epilepsy and allergy. I think these are points which are yet to be proved. There are a number of conditions, allergy may be one of them, which may have the unfortunate faculty of setting off the trick mechanism of the person who has a neurologic organization that is destined to go into convulsions.

DR. MANUEL SALL: A small percentage of epileptic patients were found to be allergic to certain proteins.

In line with the question of histaminase, I might mention an interesting case of epilepsy in which the patient was given dilantin sodium and petit mal attacks were controlled very nicely. The patient showed that she was allergic to dilantin sodium in that she responded with severe generalized urticaria to the drug and was not allergic to a gelatin capsule. A course of histaminase, 60 units a day, was given in the hope of nullifying the allergic phenomenon, but without success.

Virilism with Symptoms of Involvement of the Adrenal Cortex: Report of a Case. DR. ANTHONY P. DENOTE (by invitation).

M. C., a woman aged 23, has been in the Philadelphia State Hospital for the past nine months. This was her second commitment to an institution for mental disease, the first being to the Norristown State Hospital, from August 1935 to December 1936. The diagnosis on both occasions was manic-depressive psychosis, manic type.

There is nothing significant in the family history. The birth and early development of the patient were normal. At the age of 11 she suffered from extreme sleepiness for approximately two weeks, and a diagnosis of a "form of sleeping sickness" was made by the family physician. This cleared spontaneously, and she seemed to suffer no after-effects. At the age of 12 it was first noticed that she had an abnormal growth of hair on her face. This became progressively worse, so that its removal finally required the use of depilatories and a razor. She was self conscious concerning this growth and showed resulting definite changes in her personality, namely, seclusiveness, lack of interest in her surroundings and, finally, overactivity and overtalkativeness.

The onset of her menses was at the age of 14. The menses were regular, lasting from four to five days and occurring every twenty-eight days. Since the onset of her mental symptoms, in the latter part of 1934, her menses have been irregular.

Physical examination, made recently, showed a young woman of masculine body build with marked generalized hirsutism and an increase in muscular development. Vision was impaired because of marked myopia, which has been progressive since the age of 11. Examination of the heart, lungs, abdomen and pelvic organs revealed essentially normal conditions. Neurologic examination gave normal results. The blood pressure was 120 systolic and 70 diastolic.

Laboratory findings were as follows: The results of repeated urinalyses were negative. Wassermann and Kahn reactions of the blood. were negative. The chlorides of the blood measured 350 mg., the urea nitrogen 14.9 mg. and the creatinine 1.6 mg., per hundred cubic centimeters. The dextrose tolerance test showed an increased tolerance, the results being as follows: fasting specimen, 86 mg. per hundred cubic centimeters of blood; one-half hour, 116 mg; one hour, 96 mg.; two hours, 70 mg.; three hours, 71 mg.; four hours, 73 mg. The blood count was reported as follows: red cells 4,830,000; white cells, 10,200; polymorphonuclear cells 53 per cent, lymphocytes 44 per cent, eosinophils 2 per cent and transitional cells 1 per cent. Examination of the eyegrounds showed a high degree of myopia, with myopic changes in the fundus. Roentgenographic findings have been negative, except for increased density in the metaphysial area in a large number of the long bones. This is interpreted as manifesting a toxic reaction. A flat plate of the abdomen and an intravenous urogram showed nothing of significance. Roentgenograms of the skull were negative.

In a discussion of this case, the belief was expressed that the probability of a tumor of the adrenal cortex was sufficiently high to warrant laparotomy but that roentgen studies of the kidney region after injection of air should be performed first.

DISCUSSION

DR. HAROLD D. PALMER: Dr. DeNote has presented an interesting case and one which I believe to be important to psychiatry. The occurrence of adrenal

cortical virilism in a psychotic patient is not unknown, but many questions can be raised regarding the relation of the psychologic and the endocrine factors.

The differential diagnosis in all cases of this type is difficult, since there are several possibilities: (1) "functional hyperplasia" of the adrenal cortical tissue, (2) adenoma of the adrenal cortex, (3) a rather atypical Cushing syndrome and (4) certain mixed tumors of the ovary. Dr. DeNote has ruled out everything except the cortical adenoma, and I believe that either an exploratory operation on both adrenal regions or perirenal injection of air with roentgenographic study would be justified. In considering the etiologic factors in the psychosis of this patient in relation to the endocrine disorder, one is faced with the interesting problem of determining whether the mental reaction is totally unrelated to the condition or whether it represents a direct result of the endocrine disorder or, what is most likely, an indirect relation based on the acute self consciousness and withdrawing behavior which undoubtedly resulted from the patient's recognition of her abnormality and the difference between herself and other girls.

There is such a striking similarity between the case presented by Dr. DeNote and the case of a patient who has been under the care of Dr. Francis Lukens and myself for the last eight years that I should like to review briefly some of the characteristics of our patient. A more detailed summary of the endocrine features will be available in the June 1940 issue of *Endocrinology*.

When the girl consulted me in 1931 she was 11 years of age and had a masculine body build and a tremendous growth of hair on the face and over the shoulders, arms, back, abdomen, thighs and legs. The illness dated from an attack of scarlet fever, at the age of 7. Repeated roentgen studies, pyelograms and surgical exploration of the abdomen at the age of 12 failed to show any tumor in the adrenal region; the uterus was normal, and both ovaries were approximately of normal size. Biopsy of a specimen from one of the ovaries showed normal tissue. Amenorrhea was complete; the breasts were undeveloped, and pelvic examination disclosed an enlarged clitoris. At the age of 17 the patient was studied again, and roentgenographic study following bilateral injection of air around the kidneys confirmed the presence of a mass in the right adrenal area. In February 1937 Dr. E. L. Eliason removed a spherical adenomatous tumor, 6 cm. in diameter. The postoperative course was violent, but the patient made a complete recovery. Quantitative determinations of the estrogen and androgen contents of the urine before and after operation showed that both substances were present in enormously excessive amounts and that both returned to approximately normal levels after the operation. Another striking feature of the case was that even in the presence of the markedly masculine body development and the male distribution of coarse body hair the patient retained definite feminine psychology.

At present she is perfectly well; she has lost all the excessive body hair and part of the facial hair, and the general physical development has approximated that of a normal female of 18 years. A recent report announces that she is married and living happily with her husband.

Symbolic Art in a Case of Schizophrenia. DR. SAMUEL A. ZERITSKY.

The patient whose art productions I present celebrated his eighteenth birthday shortly after his commitment to the Philadelphia State Hospital, on March 11, 1940. Although he appears meek and seems utterly incapable of physical violence, this very boy suddenly announced to the household one day in October 1939 that he planned to murder his older brother, Bill, during his sleep with a hammer. The relatives were alarmed by this latest manifestation of his irrational behavior and caused his arrest. The psychiatrist of the Municipal Court promptly recommended that the boy be detained for observation in the psychopathic ward of the Philadelphia General Hospital pending his further disposition. Even though preliminary investigations indicated that the patient had been exhibiting evidence of a mental disorder for at least three years, his immature physical development suggested the likelihood of a hormonal deficiency, and gonadotropic substance (from

the anterior lobe of the pituitary gland and from the urine of pregnant women) was administered daily for two courses of fifteen intramuscular injections each. No noteworthy improvement in the patient's status occurred, and it was deemed advisable to have him committed.

Accompanying the records at the time of the patient's admission were a parcel of pen and ink drawings concerned with space ships and distant planets. Horrible-looking monsters were depicted in several of the illustrations, and in some instances these were pictured with long, snakelike tongues. Strangely, the patient himself expressed the somatic delusions that he had a tapeworm in his stomach which frequently invaded his throat and this caused him considerable annoyance.

Throughout the interview the patient remained with his head bowed, his eyes averted from the examiner and his lips perked up, almost like a *Schnauzkrampf*. He offered no spontaneous remarks and made but meager responses at best. When questioned concerning hallucinatory phenomena, he reluctantly admitted having heard voices some time ago but was unwilling to state whether these issued from male or female persons and pretended to have been unable to make out their actual conversation.

Because of the patient's reticence, only meager information could be elicited directly from him concerning his early development. Most of the facts were accordingly obtained from the patient's mother and siblings, who, however, discriminated as to the incidents they wished to divulge, apparently for fear of jeopardizing the patient's status. Although the family had settled in the United States many years ago, they had returned to Poland shortly before the patient's birth in order to take over a farm promised to them. The arrangements fell through and they found themselves in dire straits, finally returning to this country in abject poverty. The father began drinking heavily, his entire personality having deteriorated after this bitter experience.

In 1933 the patient's younger brother—the father's favorite child—died of pneumonia, and crazed by grief, the father committed suicide on the day of the funeral. Poverty continued to beset the family throughout the patient's childhood. He acquired a keen interest in astronomy and other sciences and frequently visited a nearby dump, where he picked up pseudoscientific publications which he read avidly.

About four years ago he began sketching in pen and ink his ideas of space ships and distant planets. Frequently he appended comments of his mental processes and described his "spiritual reaction" while under the influence of his artistic inspiration. At such moments he perceived a "crisis" in his own body which resembled, but was not quite like, abdominal cramps. He continued his drawing and writing far into the night, his family remonstrating without success, nor could his decision to give up school be overcome. His brother, Bill, as head of the household, found it impossible to control the boy and in turn became the butt of some of the more obscene pictorializations.

The illustrations became more and more symbolic as his seclusiveness and aberrant behavior progressed. In all of them, darkness, horror, monstrosities and cryptic meanings were prominent overtones. Occasional phallic symbols appeared but did not seem to possess any undue significance, except to indicate the theme of rivalry with his older brother, Bill. Interesting, although difficult to evaluate, was a set of line patterns hinting of surrealistic technic, undoubtedly intended to symbolize abstract intellectual ideas, as revealed by a code discovered in the patient's possession.

DISCUSSION

DR. O. SPURGEON ENGLISH: I have noticed that when we psychiatrists come on a patient who brings out artistic productions we are prone to cry, "Eureka! Now we understand the patient!" In my experience, I have not been able to understand much more of the patient in that way. I have to approach the problem from the opposite angle and know something of the patient's personality in order to understand his drawings. The history of this patient helps me to understand him much more than do his drawings, interesting though they are.

The patient was born when the parents were having a difficult time in Poland and were being badly treated themselves. I think it significant that this particular sibling has become psychotic, for it is known that psychotic people have had marked deprivations in their early years and have not had the necessary care, attention and emotional response from their parents in the early weeks and months of life. The boy's writings seem to show that as he grew he was a lonely little boy who had a poor relationship with his parents and with those outside the family. The very fact that his father took to alcohol and committed suicide would indicate that he did not have much emotionally to give to the world in general and to the child in particular. The mother's attitude, as you know, is rather a strange one also, as she is so distrustful of those on the hospital staff.

As late as 1938 this boy was writing fairly coherently. It appears that his favorite place to play was the dump, where he would search for magazines of weird tales. The boy has been an ardent fan of Buck Rogers and Brick Bradford. On Sunday morning he would go out, find a paper at some doorstep and follow the comic strip adventures faithfully. Thus, a rather lonely boy turned to the comic strips and magazines for an emotional satisfaction he was not getting elsewhere and began to withdraw into a world of his own—at least he went farther into a make-believe world than the average boy. In 1938 he wrote to an editor fairly coherently, proposing to write a story. He did write a story—a story of marshlands and beautiful plants, but a place in which there was no human being but himself. It is interesting that there is no color in his productions. On one occasion, I believe, he used blue ink, but with this exception he always works in black.

I showed the drawings to two of my patients who have been under treatment. Comments regarding the boy's artistic productions were interesting. One patient commented as follows: "This boy has known no love, only hate and horror. He went as far as he could until it frightened him, and one cannot keep his equilibrium in the midst of hate and horror. . ."

A great deal of the boy's art deals with faces in which the teeth are prominent, showing how his interests have not progressed far beyond orality. A great deal of the written material deals with excretions. Some of his writing contained the most obscene passages I have ever read coming from any psychiatric patient. However, in none of the material was there any mention of the opposite sex. One hears that there was reference to sexual behavior with a woman on the part of the patient's brother, but in none of his drawings or his written productions does he refer to women. This is, of course, what one would expect, for schizophrenic persons usually have a difficult time in managing their sexual adjustments.

I showed these drawings to another patient. She had read Georg Groddeck's "The Book of the It" and understood it with little difficulty. She went further than Groddeck and commented to the effect: "This boy has had a difficult birth, and he wants to get back into the womb, although getting back into the womb is frightening." (The picture of the cavern would bring this to mind.) She went on to say that he was afraid he would get violent and said that he had terrified himself into "unfeeling," that he was afraid he would be violent and hence he had to get out of the world of reality into a psychosis. He could not go on and write stories because he had scared himself into a lack of affect. (I did not know until tonight that the boy had threatened violence—threatened to kill his brother.)

To my mind, the most practical thing after all is how to gain contact with the patient. What can one get from his drawings and written productions to help in gaining access to the boy? Very little through his drawings, that is, by talking with him about his art. Efforts to reach him in this way have failed, and this is not surprising. The approach to this boy is not through his drawings. This is partly to be accounted for by the fact that the drawings were made when he was rather anxious, during what I suppose were anxiety attacks. He had not been willing to talk about them because they bring a return of his anxiety. (He reported that he had pain and fear when they were being made.)

When one has a neurotic patient with a phobia, one cannot immediately make him do the thing he is afraid of and gain his cooperation. Work with him must proceed in the direction of understanding what factors lie behind his phobia. Only later, when his confidence has been won and some understanding of the meaning of his phobia is achieved, can he be pushed into the phobic situation.

One must approach the boy at the level where he left average behavior, i. e., two years ago, when he was reading "thrillers" and Sunday newspapers. (I should read up on Buck Rogers and Brick Bradford and perhaps take a copy of amazing stories with me when I went to talk with him.) I should become interested in what he was doing two years ago, when he was writing to the editor and perhaps thinking of being a writer, but was still in the world of reality. One should try to get him to talk about Buck Rogers and the amazing world he was reading about and get on common ground with him there. Then, and only then, may one come to know what is represented in his drawings. One might be able to get him to live a more normal life and still not know all about these drawings, because they represent deeply unconscious conflicts.

DR. HAROLD D. PALMER: Has this patient had any therapy?

DR. SAMUEL A. ZERITSKY: He had treatment with gonadotropins at the Philadelphia General Hospital (in the form of a preparation from the anterior lobe of the pituitary gland and of one from the urine of pregnant women). Two courses of fifteen injections, of 1 cc. each, were given, without effect.

DR. ROBERT A. MATTHEWS: Why was he not given insulin?

DR. SAMUEL A. ZERITSKY: He was not given insulin because it was felt that the psychosis was undoubtedly of three years' duration. It was hoped that he would be helped by the hormone therapy.

PHILADELPHIA NEUROLOGICAL SOCIETY

SAMUEL B. HADDEN, M.D., *in the Chair*

Regular Meeting, May 24, 1940

Rhythmic Stimulation of the Labyrinth. DR. E. A. SPIEGEL.

While it is generally assumed that electrical stimulation of the labyrinth yields reactions only if direct (constant) current is employed, it could be shown on cats that the labyrinth responds to a rhythmically interrupted current. Binaural stimulation was used (one electrode in each external meatus) as well as monaural stimulation by a concentric needle electrode introduced into the inner ear through the bulla ossea. The latter method required smaller currents (1 to 3 milliamperes) than the former (up to 9 milliamperes) to elicit nystagmic responses of the eyeballs. With a low frequency of stimulation (1 to 5 per second) the nystagmus may show a frequency higher than that of the stimulation, reactions appearing while the current is on as well as with each break in the current. With a higher rate (6 stimuli per second or higher) the rhythm of the nystagmus corresponds to that of the stimulation. A slow and fast component may be distinguished at rates below 10 per second, while at higher rates the reaction assumes the characteristics of a fine tremor, which may be followed by a coarse nystagmus after the stimulation ceases. Definite ocular reactions in the rhythm of the stimulation were observed at frequencies up to 27 per second.

Experimental Studies on Poliomyelitis. DR. HOWARD A. HOWE and DR. DAVID BODIAN, Baltimore.

The amazing selectivity of certain viruses for particular cells points to a high degree of specificity in the chemical substrate which is necessary for virus propa-

gation. Thus in the case of poliomyelitis, apparently only the neuron furnishes the conditions under which the virus may reach a destructive concentration. In addition, only certain neurons appear to provide a medium so favorable to propagation of the virus that the latter increases to a degree incompatible with the life of the cell. The experiments to be described are concerned with the effects of certain alterations in nerve cell metabolism which change the cells from the susceptible to the resistant group. They deal with the effects of cutting the axons of two strongly predisposed cell types, the mitral cells of the olfactory bulb and the anterior horn cells of the spinal cord. The olfactory tract may be sectioned without primary damage to the bulb itself. After this operation roughly one fifth to one fourth of the mitral cells degenerate and disappear, but the majority reach a new equilibrium and persist as long as eight months. At the end of that time they are smaller and contain less Nissl substance than those of the control bulb, but otherwise look normal. When this stage is reached the bulb is refractory to infection by the intranasal route.

Within two days of section of the olfactory tract invasion of the olfactory bulb and destruction of the mitral cells usually take place to almost the same degree as in the normal bulb. Seven to ten days after operation the resistance of the bulb has increased and many mitral cells escape. After isolation from the central nervous system for fifteen to ninety days the bulb becomes almost completely resistant to virus invasion.

A similar alteration in the susceptibility of the anterior horn cells of the spinal cord was observed after section of the sciatic nerves of 17 animals. For approximately three days after nerve section the cells concerned in the formation of the sciatic nerve show little or no change in resistance to virus invasion, but within a week an increase is apparent. After thirteen to ninety-one days there is sparing of most of the motor cells on the side of operation, as compared with complete destruction on the control side. By the time function has returned to the foot muscles no protective effect is demonstrable, and the cells on the side of operation succumb to virus with the same readiness as those on the normal side.

During the period of axonal regeneration the anterior horn cells show the classic reaction of chromatolysis, and it is tempting to ascribe their refractoriness to virus to a reduction in the Nissl substance, which thus renders them a less favorable medium for virus propagation. However, during regeneration there are undoubtedly other changes of an equally profound nature which are not demonstrated by the usual histologic technics. The fact that the cells remain refractory to virus even when they contain regenerated Nissl bodies of nearly normal size suggests the existence of such alterations. The interactions between nerve cells and virus appear to be so delicately balanced that a metabolic change quite compatible with the life of the cell can bring about an almost complete reversal of its reaction to virus.

DISCUSSION

Dr. R. L. Masland: Is there any relationship between the amount of Nissl substance in a given type of cell and the resistance of that cell to the virus?

Dr. Joseph Stokes Jr.: Has Dr. Howe attempted to make inoculations with material from this resistant area to determine whether it could infect other monkeys?

Dr. Samuel B. Hadden: It is difficult to interpret and understand these interesting findings. I should like to ask Dr. Howe whether he believes that his observations may be explained on the assumption that his operation has produced a resting state in the nerve cells, during which their respiratory quotient is so lowered that the toxin or virus is unable to destroy the cells, since their powers of resistance are apparently increased. I am sure all hope that Dr. Howe's work will lead to finding out how to effect a resting state in nerve cells and thus produce resistance to disease.

Dr. F. H. Lewy: Is there any reason to believe that nerve cells in retrograde degeneration show true immunity to poliomyelitis? Viruses, as far as is known,

invade cells and multiply enormously in their interior. Is it not possible to presume that either the surface of nerve cells so changed becomes impermeable to virus or that the penetrating virus does not find conditions within the cell permitting multiplication?

DR. HOWARD HOWE, Baltimore: In reply to Dr. Masland's question suggesting the relation between Nissl substance and cell resistance, I should state that this was an idea which we played with for some time in the beginning, but for which we could not find any real proof. For example, mitral cells in the olfactory bulb appear to be relatively poor in Nissl substance, but they are rather susceptible to virus. However, so little is known of the degree of dispersion of Nissl substance in cells that comparisons mean little.

I am a bit wary of the method of virus assay, as mentioned by Dr. Stokes. It is possible that it is not delicate enough to show what one wants to know. If one did make inoculations with material from the resistant area and obtained nothing one could not conclude that there was no virus there. One really needs a histologic method of demonstrating virus.

Dr. Hadden suggested that the cells in question are in a resting state. I do not think so. Actually, they are growing axons as rapidly as they can. They have changed their metabolic state and are now growing. They may not be conducting; nevertheless, they are definitely active during the phase of regeneration.

Apropos Dr. Lewy's inquiry, it is possible that the virus may enter these cells but not kill them. We have no evidence on that point.

Rickettsial Meningoencephalomyelitis. A Histopathologic Study of a Case of Rocky Mountain Spotted Fever. DR. H. EDWARD YASSKIN, Camden, N. J.

The rickettsial diseases of man include a number of tick, louse, flea and mite-borne diseases caused by infectious agents termed rickettsias. The known characteristics of these micro-organisms suggest that they may be a group intermediate between bacteria and filtrable viruses.

The two rickettsial diseases which are prevalent in the United States are endemic typhus and Rocky Mountain spotted fever. The latter is the more important economically and the more widespread disease of the two.

Since the identification of Rocky Mountain spotted fever in the East by Badger, Dyer and Rumreich (*Pub. Health Rep.* **46**:463 [Feb. 27] 1931) the frequency of recognition of the condition in the eastern states has steadily increased. In the spring and early summer of 1938 an outbreak occurred in New York and New Jersey which was characterized by great morbidity and fatal termination in many of the cases. The mortality in the East has been estimated to be about 25 per cent. In New Jersey in 1938, 7 deaths occurred in a series of 15 cases reported, giving a mortality rate for the disease of 46.6 per cent in that year. The continued recurrence of the condition, together with an increase in the number of cases reported, makes one believe that the disease not only is established permanently in the East but may become more widespread.

Spotted fever is primarily a disease of rabbits and rodents. It is caused by a rickettsial organism named Dermacentroxenus rickettsi. The rickettsias are conveyed from infected animals to man by certain ticks. The chief vector in the East is the dog tick (Dermacentor variabilis). Human beings are infected by the bite of the adult ticks. The causative rickettsial organisms are intracytoplasmic viruses. They primarily affect blood vessels and produce a specific pathologic lesion characterized by inflammation and thrombonecrosis of arterioles and venules. The virus has the tendency to invade the endothelial and smooth muscle cells of the smaller blood vessels of nearly all types of tissue.

REPORT OF CASE

The patient on whom necropsy was performed was residing in Long Island, N. Y. at the time she became ill. Her clinical course was fulminating, and she

died ten days after her admission to the hospital. The diagnosis was established ante mortem by means of repeated positive Weil-Felix agglutination reactions, guinea pig inoculation and cross immunity tests.

Postmortem Examination.—The brain was congested and rather soft. The meninges were thickened and dull and had lost their normal glistening color. No further abnormalities were noted.

Microscopic Examination.—Sections of the cerebral cortex, thalamus, basal ganglia, brain stem and cerebellum were studied. These sections revealed lesions which fall into three general classes: (1) inflammatory lesions involving the vessels and their sheaths; (2) focal and diffuse proliferative lesions in the brain substance, and (3) focal necrotic lesions mainly within the white matter of the cerebral hemispheres and brain stem.

The vascular lesions which were present in the cortex, subcortex, brain stem and cerebellum were of varied nature. Some vessels showed slight to dense perivascular infiltration with monocytic and lymphocytic cells. The arterioles were the radicles most often affected. Some of the smaller vessels showed occlusion either by proliferation of the endothelial cells or by central thrombi. Focal hemorrhages were noted, especially in the pons and medulla. Marked necrosis of the vessel walls with a layer of inflammatory cells surrounded by a glial syncytium was occasionally seen.

The proliferative reaction was evidenced by accumulation of glia cells along the sheaths or adjacent to vessels showing endothelial changes and thrombosis. Small nodular collections of glia cells were noted in, or adjacent to, lesions of capillaries and precapillaries. Sections stained with Globus modifications of the Cajal gold chloride–mercury bichloride method and with Hortega silver stains demonstrated diffuse gliosis in sections of the cerebral subcortex, basal ganglia and thalamus. Focal astrocytosis was seen adjacent to thrombosed and necrotic vessels.

The third type of lesion of the brain was the most prominent and characteristic. This lesion was a circumscribed area of rarefaction and vacuolation of brain substance. These focal necrotic areas were widespread in the white matter of the cerebral hemispheres, cerebellum and thalamus and were less marked in the sections of the brain stem. Most of these lesions were in close association with partially or completely occluded vessels. The relation of thrombosed, necrotic vessels to areas of necrotic brain tissue seemed to indicate that the necrotic lesions were infarctive and dependent on local vascular injury. Weigert and Spielmeyer stains revealed these lesions to be focal areas of demyelination and destruction of axis-cylinders with suggestive perivascular distribution. Scarlet red stains of sections containing the necrotic lesions revealed gitter cells laden with coarse fat drops in these areas. This third type of cerebral lesion appears to be characteristic of the eastern form of Rocky Mountain spotted fever and may prove to be a reliable histologic criterion for the differential diagnosis of the disease and typhus fever.

The cerebellum, in addition to the lesions described, showed marked infiltration of monocytes and lymphocytes within the pia-arachnoid.

The paper will be published in the *Journal of the Mount Sinai Hospital.*

DISCUSSION

DR. F. H. LEWY: I should like to ask Dr. Yasskin whether he did not find Fraenkel's nodules, which are a characteristic and common pathologic sign in human and experimental spotted fever.

DR. H. EDWARD YASSKIN, Camden, N. J.: The nodules which Dr. Lewy referred to have been described as a characteristic lesion in typhus fever encephalitis. Although such small glial accumulations were noted in the sections of my case, they were not prominent. The characteristic feature of the encephalitis associated with spotted fever was the circumscribed areas of thrombonecrosis with evidences of generalized as well as focal astrocytosis.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

LINUS J. FOSTER, M.D., *President, in the Chair*

Regular Meeting, Sept. 19, 1940

Occupational Therapy in a State Hospital. DR. H. C. DUNSTONE, Ypsilanti, Mich.

The various types of occupational therapy available in the Ypsilanti State Hospital are reviewed. The placement of patients in these endeavors is discussed from the standpoint of the underlying dynamic psychologic factors involved. Depressive reactions in manic-depressive psychoses and involutional, psychoneurotic and schizophrenic reactions are illustrated by responses to work of various types, such as the patient's reaction to the work, the gradual progression from depression to normality, the type of work that the patients wish to do and the results of undirected art work. The projections of the delusions of a paranoid schizophrenic patient are illustrated in his wood carving, clay modeling and crayon work. The similarity of therapeutic occupational patterns in alcoholic, paranoid and homosexual patients is pointed out. A plea for a scientific approach to this time-tested therapeutic method is made. Typical examples of all forms of occupational therapy products illustrate the points made.

DISCUSSION

DR. THOMAS J. HELDT, Detroit: As Dr. Dunstone has so ably outlined, these manual creations depict many of the patients' painful repressions, morbid complexes and static activities. Occupational therapy so encouraged and fostered gains a kinship with the release therapy described by David M. Levy for children, and even with the release activity expressed by a patient in the toxic delirium associated with sodium amytal narcosis.

A Study of Alcohol and Its Relationship to Carbohydrate Metabolism. DR. F. W. PALMER, Ypsilanti, Mich.

Chronic alcoholic and nonalcoholic persons were placed on measured high carbohydrate diets, and their carbohydrate tolerance was measured on two or more occasions by means of a standard carbohydrate tolerance test. In addition, ethyl alcohol was given in a similar carbohydrate tolerance test in an endeavor to find if there was any change in the utilization by these persons of carbohydrate in the presence of alcohol.

No consistent individual variations in the carbohydrate tolerance under the influence of alcohol were found. Group averages for each group and for the entire group studied showed no significant variation from a normal response to the ingestion of a standard quantity of carbohydrate. Blood alcohol tolerance curves determined simultaneously were comparable for each group.

DISCUSSION

DR. L. H. NEWBURGH, Ann Arbor, Mich.: The first difficulty with the interpretation of dextrose tolerance tests is that most of them have been improperly performed. As long ago as 1890, Hoffmeister began talking about fasting diabetes. He pointed out at that time that the dog deprived of food showed a marked falling off in utilization of dextrose. Since then many workers have shown that a diet low in carbohydrate lessens the utilization of dextrose by the human being. For these reasons my associates and I insist that every patient in our clinic who is to have a dextrose tolerance test take a diet containing at least 300 Gm. of carbohydrate for five days preceding the test.

Dr. Palmer has also followed this procedure. He finds that the tests gave normal results in patients with chronic alcoholism. One conclusion to be drawn from these studies is that these patients are not suffering from cirrhosis of the

liver. All are familiar with the teaching that the chronic use of alcohol is a common cause of cirrhosis. Within the last few years this has come to be doubted, and here is further evidence that alcohol does not commonly produce cirrhotic changes in the liver. I say this because disease of the liver of any type will interfere with the utilization of dextrose, if the disease is at all advanced. The dextrose tolerance test properly executed is probably as good a test of hepatic function as one has.

Dr. Thomas J. Heldt, Detroit: Dr. Palmer's clearcut data stimulate further inquiry. What is the time correlation between the maximum height of sugar and that of alcohol in the blood after the injection of carbohydrate and ingestion of alcohol? What is the average length of time for the appearance of alcohol in, or its disappearance from, the blood after the intake of alcohol? In his experimentation, Dr. Palmer has consistently and appropriately used absolute ethyl alcohol. I wonder how his deductions might have been changed if he had used ordinary commercial grain alcohol. How safely may some of the deductions be applied to the ordinary alcoholic patient? In his study of the problem, has Dr. Palmer perchance discovered any data relating to the intake of chemically pure ethyl alcohol by human subjects, experimentally or otherwise? It seems reasonable that in the study of alcoholism one must take into account fusel oil adulterants. Hence, in a study of the incidence of damage to the liver one should not fail to take into account isoamyl alcohol, methylethylcarbincarbinol and the other higher alcohols that may be present in varying amounts in alcoholic beverages.

Dr. Russell T. Costello, Detroit: My colleagues and I have noted that in the chronic alcoholic patients who came to us there was marked enlargement of the liver, which, if they stayed long enough, subsided in about ten days. I feel that when the liver is thus enlarged, hepatic tests should be made within that period.